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CHEMICAL AND MOLECULAR PROCESSES IN CONTRACTILE ACTIVITY

W. F. H. M. MOMMAERTS, Ph.D.
Cleveland, Ohio

ANY MODERN DISCUSSION on the chemical and molecular nature of cardiac activity is largely based on the presumed analogy between the processes in the heart and those in striated muscle. This is due to the circumstance that, while skeletal muscle has been the classical material for those biochemical researches which lead to present-day knowledge concerning myosin, actin, phosphocreatine and adenosine triphosphate (ATP), similar experimental investigations on cardiac muscle have been carried out only sporadically. While an upsurge of interest in this direction has become noticeable, we still have to lean heavily on information derived from skeletal muscle.

The chemical physiology of the heart seems to stand by itself only in one respect, namely, with regard to those processes which cause its automaticity. Morphologically, this regulation is ascribed to the nodal and conductive tissues. There has recently been an increased interest in the biochemical investigation of these tissues, as evidenced by valuable reports on its ionic composition (Davies, *et al*) and its lipid content (Robb and Mallov). In view of the resemblance between its task and that of nervous tissue, and of the importance of the acetylcholine system in the generation and conduction of impulses in the nervous system, we have recently investigated the distribution of cholinesterases in the heart. It appears that the myocardium contains an unspecific cholinesterase, while the Purkinje tissue is endowed with the specific acetylcholinsterase commonly found in nerve. This enzyme is characterized by a high rate of splitting of acetylcholine and, to a lesser extent, of β-methylacetylcholine; by a characteristic dependence of its activity upon the substrate concentration; and by its inability to hydrolyze butyrylcholine and benzoylcholine. The enzyme was found in the bundle of His and the AV-node in about the same amount as in typical peripheral nerve, and occurs also, in about half the concentration due to the admixture of connective tissue, in the moderator bands.

Returning now to the chemistry of the myocardium, the first question to be discussed is its dependence upon continuous aeration. Incorrectly, this is sometimes regarded as a sharp difference between cardiac and voluntary muscle. The purpose of metabolism—whether respiratory or glycolytic—is to generate high-energy phosphate compounds, primarily ATP. Much more ATP is generated by aerobic than by anaerobic dissimilation of foods. There are types of muscle which are well provided with all the enzymes involved in tissue respiration and aerobic phosphorylation, such as cytochrome oxidase, cytochromes, flavin enzymes, et cetera; sufficient to resynthesize ATP at the same rate as it is used in the highest activity of the organ. The heart is an example of such muscles, but there are many instances among skeletal muscle as well. Since in these cases, respiratory metabolism is so well developed, and is supported by an ample circulatory oxygen supply, no need arises for additional metabolic pathways like glycolysis. On

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the other hand, there are muscles which function only intermittently, in periods of high activity but short duration. These are usually not well endowed with respiratory enzymes so that during intense activity the consumption of ATP far exceeds its respiratory resynthesis. Such muscles usually possess an active glycolytic enzyme system, which delays the exhaustion of the energy-rich phosphate compounds without being able to prevent it in the long run. These muscles are therefore not able to work at a high rate for unlimited periods, while in the former group a stationary balance between energy output and metabolism can be maintained. That the heart belongs in this group for functional reasons is obvious, but clearly its metabolism does not set it apart from all other muscles.

We have already referred to the fact that ATP is used in contractile activity. This important insight rests first of all upon the results obtained in the laboratory of O. Meyerhof, up to the late 1930's. As other substances such as lactic acid and phosphocreatine, became eliminated as the direct causative agents of contraction, ATP remained as the substance which, as far as one could tell, must be directly linked with the contractile process.

To cause contraction, or to provide energy for it, ATP must interact with the contractile structure which we may presume to be of protein nature. While there is a large number of different proteins in the sarcoplasm, the protein composition of the fibril is fortunately much simpler. For a time, the contractile filaments were even believed to consist of one protein only—myosin. A fundamental study by Von Muralt and Edsall (1930) revealed that this protein displays the property of flow-birefringence, which suggests that it consists of very long molecules or particles, well suited to build up a fibrous structure. Weber prepared myosin threads by extrusion into a precipitating bath of dilute KCl; these threads are good optical models of the anisotropic bands of the muscle fibril. In 1939, it was then found by Engelhardt and Ljubimova that this structure protein has enzymatic activity in that it acts as an adenosinetriphosphatase, myosin-ATPase. This was a discovery of great importance—quite independent of our eventual judgment concerning its direct physiological meaning—since it pointed for the first time to a concrete connection between energy-yielding reaction and contractile structure. The same authors as well as Needham *et al* (1942), also discovered that ATP exerts some physical effect upon myosin.

These important indications were fully explored in the classical investigations of A. Szent-Györgyi and his school, beginning in 1940. It was found, first of all, that myosin in the older sense is not a well-defined substance, but that products of highly different behavior can be obtained. dependent on such seemingly trivial details as the duration of the extraction or the degree of mincing of the tissue. Short extraction of coarsely ground muscle with 0.5 M KCl yields a product which approaches what is now known as myosin itself. This was crystallized, with some denaturation, by Szent-Györgyi, and was prepared in entirely pure form by Weber *et al,* and by Mommaerts and Parris. Myosin consists in all probability of rod-shaped molecules of 160 mμ. long, with a molecular weight which is estimated as 850,000 in Weber's laboratory and 650,000 in ours. Prolonged extraction of minced muscle, on the other hand, leads to the appearance of a complex protein, actomyosin, in which myosin is combined with actin, discovered in Szent-Györgyi's laboratory by Straub. Actin is a protein which can exist in the form of globular molecules (G-actin) or as a fibrous modification (F-actin) originating by polymerization of the globular form. In actomyosin, myosin molecules are randomly attached to the strands of F-actin, while in the muscle fibril, the two proteins apparently are arranged parallel in a highly organized structure. These same proteins also occur in the heart, but their study in this case has considerably lagged behind. Actin and myosin constitute the bulk of the contractile structure, but other proteins such as tropomyosin (Bailey) or Y-protein (Dubuisson), of unknown function, may occur in the fibrils in smaller amounts. That actomyosin is the material substrate of contractility will be documented later; in addition, its participation in contraction is also suggested by the observation of Dubuisson that it is temporarily rendered insoluble in shortened muscle.

The second important discovery by Szent-Györgyi was that both myosin and actomyosin have ATPase activity, but that only actomyosin is strongly affected by ATP in its physical behavior. The influence of ATP can be detected in

actomyosin solutions by physical measurements, but shows very striking manifestations in precipitated actomyosin systems. Going from the lowest to the highest forms of organization, these actomyosin systems present the following features.

In suspension, flocculated actomyosin becomes denser, because the individual flocks contract and expell water, a phenomenon called supercontraction by Szent-Györgyi. Under some conditions, the individual flocks adhere, and the entire system shows strong synaeresis.

Threads of actomyosin contract upon the addition of ATP to one-third of the original length. The thickness decreases equally, since there is little preferred orientation in the threads, but by rolling and stretching they can be made to contract preferentially in a longitudinal direction.

Threads that contract only lengthwise, becoming thicker when shortening, and that can lift a load, have been prepared by controlled drying of an extruded thread (Weber) or by compression of actomyosin layers spread on a water surface (Hayashi).

Finally, Szent-Györgyi has introduced a preparation of fiber bundles from the *musculus psoas* of the rabbit, extracted in the cold by aqueous glycerol. This is a preparation which contains actomyosin in its original orientation without prior dissolution, but from which most other active constituents are removed in the extraction process. Such fibers likewise contract lengthwise and develop tension, and this tension is equal to the maximal tension of the muscle from which they are derived. Similar preparation obtained from cardiac muscle have been studied by Taeschler and Bing.

Last but not least, Marsh and Bendall have discovered that when such contracted fibers are treated with ATP in the presence of a water-soluble muscle protein, they can be made to relax again. In investigations by Bozler and by Goodall and Szent-Györgyi, relaxation has been obtained by means of phosphocreatine, but this too seems to depend upon the participation of the Marsh-Bendall factor, and, since phosphocreatine may phosphorylate a nucleotide retained in the fibers, it does not necessarily cause relaxation by itself.

In this series, we have arranged the actomyosin systems according to increasing perfection of their molecular organization. In the flocks and extruded threads, the actomyosin particles are unoriented and are held together by few random weak links. The better the parallel orientation obtained, and the stronger the cross linkage achieved, the more will the systems resemble *in vivo* contraction. Throughout the series, salts play a decisive role: a basic concentration of KCl is always added, while Mg promotes and Ca counteracts the contraction. One remaining discrepancy should not remain concealed: the contraction and relaxation phenomena *in vitro* are very slow, requiring minutes instead of fractions of a second, and this difference does not seem due entirely to diffusion of the ATP. We may hope that also this detail will eventually be understood; otherwise, the results will speak for themselves.

While these achievements have gone far in answering the question as to what causes and constitutes contraction, we also have to investigate how fast, by what amounts, when, and how these effects are brought about.

On another occasion, I have given some quantitative statements regarding the metabolic changes correlated with muscular work. It was found that the activation of one gram of muscle involves the breakdown of 0.25 to 0.3 μM. of ATP, and up to 0.5 μM. under conditions of maximal work. Further, it was derived that continuous activity, for example, a tetanic contraction of striated muscle, involves a steady breakdown of ATP, the rate of which depends on the type of muscle, but which may be of the order of 1 mM. per gram per minute for average mammalian muscle in tetanus, and up to about one-tenth of this for the myocardium in extreme activity. Any biochemical mechanism proposed must be in accordance with these estimates.

It is partly in the light of these estimates that I have criticized a too eager acceptance of myosin-ATPase as the *Deus-ex-machina*. The activity of this enzyme depends enormously on the pH and ionic composition of the medium—a fact which makes it very difficult to estimate its possible activity *in vivo*. But doing the best we can, the conclusion is obtained that myosin-ATPase can explain 1 to 2 per cent of the actually occurring rate of breakdown in muscular activity. This conclusion, which is largely based on the strong inhibition of myosin-ATPase by magnesium, has not been generally accepted by other workers in this field. Some o fthem point out that there are cases in which Mg does not inhibit the ATPase; even activations have been reported. But such ob-

jections have never been made in quantitative form, and it is not realized that such activation effects have hitherto been found only when the basic activity is very low, for example, at pH 7 in the absence of Ca. Our views have, for instance, been strongly attacked by Hasselbach who described that his actomyosin preparations are activated by Mg, but overlooked that his activated preparations were no more potent than our maximally inhibited ones. I maintain, therefore, that myosin-ATPase cannot be relied upon to explain the events *in vivo*.

An entirely new viewpoint has come from the study of actin. This protein has some remarkable properties, early recognized by its discoverers. While in aqueous solution, it shows no abnormal behavior, but after the addition of salt, its solution becomes extremely viscous and strongly birefringent. As mentioned before, actin occurs in the form of single globular molecules (G-actin) in water, but upon the addition of salt it polymerizes to F-actin. Recently, Straub and Laki and their collaborators showed that actin preparations contain ATP, and that without this substance actin connot polymerize. Following this development, I prepared pure actin by ultracentrifugal isolation of F-actin from a crude extract, followed by depolymerization in the presence of ATP. With pure actin, the mechanism of the polymerization reaction could be investigated quantitatively, and it was found that the following stoichiometric equation holds:

$$\text{actin} + \text{ATP} \rightarrow \text{actin}_{(\text{polym.})} + \text{ADP} + \text{P}$$

This result not only opens up the study of the mechanism of this striking molecular transformation, but has also a direct physiological consequence. For the stoichiometrical proportions are such that if all the 30 mg. actin (mol. wt. about 57,000) in one gram muscle would polymerize once, it would dephosphorylate exactly the 0.5μM. of ATP which, as calculated previously, activate one full twitch of this amount of muscle. This identity suggests strongly that the polymerization of actin is one of the elementary reactions in activity, and is possibly identical with the "fundamental process" of Gasser and Hill which precedes the macroscopically visible contraction and coincides with the initial heat production. The actin polymerization, furthermore, can be very fast, although it has not yet been possible to estimate its actual speed under conditions like those in muscle.

After these observations regarding speed and amount, we can turn to the question, "When?" referring to the problem of the sequence of events in contraction, investigated, by physical means, with such high perfection by A. V. Hill. The occurrence of polymerization of actin during the activation phase is only a hypothesis. Even the all important question of whether ATP is indeed broken down during contraction has never been decided. Encouraged by a recommendation from Hill that the relatively slow skeletal muscles of turtles should provide a favorable material in which to investigate this phenomenon, we have given considerable time to developing a method permitting the instantaneous cooling of such a muscle at any desired phase of contraction. This is achieved by high-speed immersion of a contracting and a control muscle into liquid propane cooled to 90° absolute temperature by which very rapid cooling is obtained. With this method, the sequence of chemical and structural changes is now being investigated.

There remains, then, the final question, "How?" referring to the actual molecular mechanism of the contracting process. I feel strongly that, as long as the preceding questions have not been answered, this last one is altogether too ambitious. Theories about the mechanism of contraction are, at best, fascinating intellectual exercises as long as the basic facts are not yet known.

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SOME CHEMICAL ASPECTS OF THE CONTRACTILE MATTER OF MUSCLE

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CLASSICAL HISTOLOGY provides a clear picture of the striated muscle fiber as it appears externally. A long sarcolemmal sheath contains material which displays regular striations. The histologist describes the muscle fiber as composed of repeating units of relatively isotropic bands (I) and optical anisotropic bands (A). A membrane or band Z bisects the I band and another band M bisects the A band. The finer details which can be seen using the electron microscope will not be discussed here.

The complex architecture of the cross striated muscle and its alterations in various physiological states has led to many theories about the localization of the different substances in the bands. The interest in this question is due to the fact that the visible alterations are considered to furnish clues regarding the contractile mechanism. Muralt and Edsall[8] tentatively suggested after having demonstrated the double refraction of flow in actomyosin solutions that the actomyosin was located in the anisotropic band. Schmitt *et al.*,[5] considered from investigations on formalin fixed material that the fibrils were composed of actomyosin threads. The relative isotropy of the I band was ascribed to a lack of preferred orientation in this region or to some substance compensating the double refraction in this band. Our experiments have led to a somewhat different conclusion.

We have tried to prepare non-fixed myofibrils by using the following method.

The myofibrils were prepared from rabbit skeletal muscle which were minced in fairly large pieces in a cooled mincer. A cooled isotonic buffer solution was added and the minced muscle was ground in a cooled mortar. The mass was suspended in more cooled buffer solution and centrifuged for a short time. The precipitate was discarded and the particles in the supernatant solution were spun down in the centrifuge and resuspended in cooled isotonic solution.

Investigations with a common light microscope showed that the solution contained ribbon like particles with the characteristic cross striation in a fairly pure state which also was shown by an inspection in the electron microscope. The figure shows a bundle of such fibrils at low magnification. No staining has been used. The white bands are the anisotropic ones. From the picture it can be seen that the electron scattering mass is far greater in these bands than in the isotropic bands. This is an indication of an uneven distribution of material. The different bands had about the same length 4μ showing that the contraction must have been small. When a small amount of ATP was added, they contracted violently. I think that they can be considered as part of the structural elements of the muscle.

The following analyses have been made on these fibrils. When they were suspended in 0.5 M KCl for a short time nearly all of the isotropic bands went into solution but the anisotropic bands remained. An inspection in the electron microscope showed that generally little of the material in the isotropic bands was left. From the appearance of the material in the anisotropic bands it could be recognized as being F-actin. It was also found possible to bring into solution the remaining anisotropic bands either by using 0.5 M KI or a pH of about 9, methods well known for bringing actin into solution.

The nitrogen ratio of the two solutions thus obtained was determined. The ratio was $N_{KI}/N_{KCl} = 1.97$. This is in rather good agreement with the result of Engström[1] using x-ray absorption measurements. He found a mass ratio of 1.8 for A/I using the sheath of the striated muscle from Chironomus larvae.

A determination of the phosphorus ratio has also been made. This ratio was 3.70. I think that all the phosphorus is not so firmly bound so this value is probably too low. The figure shows, however, that the greatest part of the phosphorus is bound in the A band. I believe nevertheless that some of the phosphorus really is bound in the I band too, probably as nucleoprotein, the latter conclusions is arrived at in terms of ultraviolet absorption measurements.

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Our results indicate that the actin together with the greater part of the phosphorus is in the A band in the resting state. During the first phases of the contraction the substances move (probably the actin[13]) and unites. An indication that such is indeed the case follows from the fact that on raising the temperature of the fibril suspension the formerly KCl soluble substance no longer goes into the solution on short KCl treatment. This behavior could be accounted for if actomyosin were formed under such conditions.

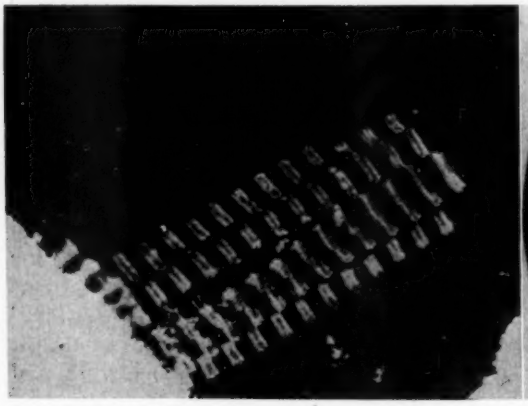

Fig. 1. Electron micrograph of a bundle of muscle fibrils. No staining (x 2 600).

Fig. 2. Electron micrograph of an extracted muscle fibril. The isotropic band extracted with 0.3 M HCl. Gold-manganine shadowed (x 7 200).

In the case of the skeletal muscle the greatest part seems to be myosin in the I band even if, as is probable, some other substances also occur. In such a case, chiefly, actomyosin is built up during the contraction process which in turn probably then reacts further.

Up to the present time heart fibrils have not been investigated extensively. They are more difficult to obtain in a pure state. We must therefore be a little more cautious in making statements about the nature of the substance in the isotropic bands in such tissue, even if the fibrils are cross striated. From other investigations we have observed that myosin and actomyosin can only be obtained in relatively poor yields.[2] If the heart muscle is more finely divided, another contractile complex is easily extracted. This complex, we have called actotropomyosin.[11] Our investigations on that complex are, however, mainly done on actotropomyosin extracted from a gravid uterus where it predominates. Our analyses indicate that actotropomyosin is composed of actin, a protein which we have called the phosphate-absorbing protein and tropomyosin mostly as nucleotropomyosin. It may be that in the case of the heart, the isotropic band contains much of the nucleotropomyosin and the phosphate-absorbing protein in a complex. Further studies must, however, be done to elucidate the questions concerning this complex in the heart.

It seems to me that the problem of contractility is connected with structure and alterations in structure. If we want to approach the problem on a molecular level we have (during the first phases) to think of alterations in the structure of the actin. During subsequent phases in the muscle action, alterations in the molecular structure of myosin or the tropomyosin-complex, may also be of importance.

Concerning the actin it is known that it can go from the molecular state of G-actin to the associated form, F-actin. It contains ATP in the G-state and liberates one phosphate (in solution) whence it goes over into the F-state containing ADP. This reaction occurs rapidly when some salt is added to the solution. Under certain circumstances the reaction can be reversed by adding ATP. Straub[14] was the first to show this, followed by Laki[6] and Mommaerts.[7]

Schematically the reaction, following Laki, can be written: G-actin ATP $\rightleftharpoons$ G-actin$\sim$P ADP$\rightarrow$ F-actin ADP+P

It seems, however, very unlikely to me that only a split of the phosphate residue would take place without the energy rich phosphate bond

being used in a chemically satisfying way. It is therefore unsatisfying to think that, for example, that the formation of any serine-phosphate bond in the actin plays a rôle. Such a bond as it occurs in casein, is too stable.

It is more probable from the general behavior of ATP that a certain substance in the actin reacts with the energy rich phosphate and in that manner raises the actin up to a more reactive level. Also in this reaction divalent ions ought to take part as is usually the case when ATP participates in a reaction. This is also indicated by the fact that the reaction is inhibited by chelating agents.

We have tried for a long time to find in the actin the substance responsible for the reaction. I think now that Dr. Gelotte,[3] during his last time in my laboratory brought evidences for the existence of a substance (X) of low molecular weight nature in the actin. He succeeded in isolating it from purified F-actin by repeatedly shaking it with water and chloroform. In the first water extract, adenine nucleotides and sometimes even hypoxanthine derivatives are obtained in large part. The adenine derivatives are loosely connected with the actin and it is also possible to get rid of them before the experiment. Later on the prosthetic group of the actin appears. It is thus much more firmly bound. The adenine nucleotides are bonded to the actin in much the same way as a substrate molecule is bonded to the special surface of an enzyme. It may be mentioned at this point that the actin contains between 1 to 2 per cent of the new substance calculated on the basis of dry weight.

We have not as yet been able to prepare the new substance (X) in quantities sufficient to enable a determination of its constitution. It has up until present time given much trouble during our investigations because it appears in several forms. Some of them are obviously associated forms. They have also different ultraviolet spectra and can be transformed reversible one into the other. One form, which we think is a kind of monomeric form, has the ultraviolet spectrum given here. Another form can be prepared unassociated with any ions and that form has no maximum in the ultraviolet up to 210 mμ.

Obviously the presence of divalent ions in the substance (X) plays an important role in its reactivity. When possessed of its ions it spontaneously reduces silver nitrate. On the other hand, however, when devoid of its ions or if heated up to boiling point in solution prior to silver nitrate treatment, it cannot reduce it. From the infra-red spectrum it can be concluded that it contains labile carbonyl and amine groups and that it is not an aromatic compound.

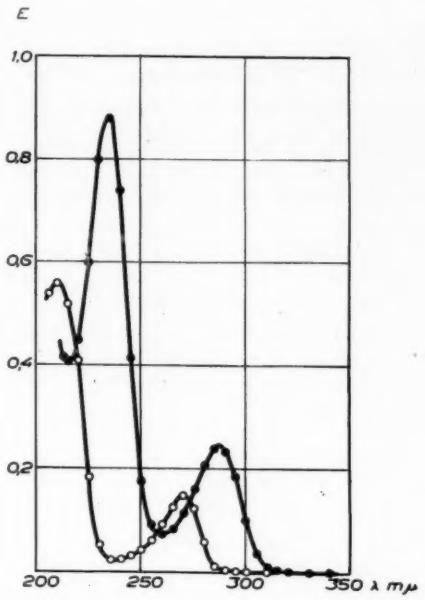

Fig. 3. Ultraviolet absorption curve for the substance (X).
Open circles: in 0.01 M HCl.
Solid circles: in 0.01 M KOH.

These investigations should give a clue to the dependence of the actin on its divalent ions and on energy rich phosphate when they are finished.

The reaction of the actin seems, at the present time, to be peculiar in many ways. One actin molecule reacts with ATP as an enzyme but at the same time it can react with other actin molecules going over to an associated state that is not enzymatically reactive as a phosphatase. This probably depends on the manner in which the reactive substance (X) is bound to the actin. However, with some alterations in the bonds it can be supposed that the actin can act only as a phosphatase.

In this connection I want to discuss another protein which we have found, and which may be derived from the actin in just such a manner. It is the phosphate-absorbing protein that has been prepared from the heart[4] and from the uterus,[12] and is connected with the actotropomyosin complex. I am inclined to consider it (in the free

form) as a partly denatured protein but even so it shows some interesting properties. It contains about 10 per cent nucleotide material originating from derivatives containing the substance (X). We consider it, therefore, as derived from the actin. The protein takes up phosphate but only from ATP. It does not associate as actin does.

This phosphate uptake from ATP is probably a residue of its former phosphatase activity which is lost during its preparation. Actually when newly prepared it has a very rapidly lost phosphatase activity. When this protein is in the actotropomyosin it obviously acts as a phosphatase together with the nucleotropomyosin while this system reacts quite as actomyosin. On addition of ATP to an actotropomyosin solution and spinning down the actin the phosphate absorbing protein is found with the nucleotropomyosin in the supernatant.

When preparing the nucleotide material from the phosphate-absorbing protein there was one component of special interest which comes out from the ionic exchanger as one sharp peak containing some phosphorylated compound. A paper chromatograph was made on this using amyl alcohol-phosphate buffer. There could be distinguished six different spots with R_f-values of 41, 49, 57, 64, 69, 78. The spectra of them indicate that they can be related in the same sequence to guanine, xanthine derivatives, hypoxanthine, two derivatives which resembles guanosine and inosine and at last one uracil derivative It can be mentioned that as a certain component on the anionic exchanger a phosphorylated uric acid derivative also appeared. All these derivatives of oxy pyrimidines and purines seems to have the same origin of phosphorylated derivatives with the substance (X). That such a suggestion can be made is revealed also from certain features in the infra-red spectrum from one form of the substance (X).

It seems that the transformation to hypoxanthine and the inosine resembling derivative can occur easily. I think that sometimes when hypoxanthine has been observed in solutions of the contractile matter it can have its origin from such transformations. Therefore, it is not for the moment possible to say when a real deaminase effect has been observed.

Our investigations[9] of the action of cardiac glucosides on the contractile proteins have been quite superficial thus far, for we are in the orientation phase, trying to find the right starting point for the chemical aspect of the problem. The cardiac glucosides have certainly (beside other reactions) a direct influence on the contractile element, that is, reversing the bonding of ions in the contractile system and in that manner influencing the ionic balance in the environment of the muscle fibril.

The function seems to be a regulatory one in which the reactive substance (X) is maintained in an appropriate state by adjusting its ionic bonds in a steady state condition. This view is one which must be made the subject of some future detailed study.

In fact there is already some indication that the cardiac glucosides can act in this manner. We have observed that when a fresh anionic exchanger was used we did not obtain the form of the substance (X) which we have called the monomeric one, this being true even if we started with that form. Using a resin which had been used before, this alteration did not happen. This can be related to an exchange of ions brought about by the resin. If we started with a sample of substance (X) previously treated with cardiac glucosides the monomeric form was obtained even if a fresh resin was used. It seems, therefore that the cardiac glucosides can preserve the reactive substance in an appropriate state and that it acts so when the substance (X) is coupled to protein.

In our investigations of heart actin from cattle prepared according to Straub the preparations were made some hours after the death of the animal. This actin was contaminated with actotropomyosin which was partly degraded. This so-called actin did not associate in the usual way characteristic of skeletal actin when salt was added. An investigation in the electron microscope showed that the actin had formed clusters.[10] On adidtion of cardiac glucosides it associated rapidly to F-actin. On the same kind of actin we observed on investigating the dialysis water that also hypoxanthine derivatives were given off. On using an actin solution which was treated with cardiac glucosides merely adenine derivatives could be detected in the dialysis water.

It remains to be shown how these effects are related. When the actin was treated with alcohol we got an actin solution which did not give off any hypoxanthine derivatives; nevertheless the actin did not associate unless cardiac glucosides were added.

It thus seems that the cardiac glucosides are

involved in several of the reactions and that they can do this even in the very small quantities used may depend on the fact that their action is directed against one and the same substance at least in these *in vitro* experiments. We believe that this is the new substance (X) which in different states conjugated to protein can show both ATP: ase property and be transformed in any purine derivatives.

Evidently, our present observations open a path which, when sufficiently traveled, will enable us to learn something about the mode of action of the cardiac glucosides on the contractile element.

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Discussion

VICTOR LORBER, Minneapolis, Minnesota.—How chemical energy is converted to work in living systems constitutes one of the fundamental problems of biology and medicine. The papers presented by Dr. Mommaerts and Dr. Snellman have indicated the direction which the work on this problem is taking in muscle, where it has been studied most intensively and fruitfully. Much detailed information is at hand concerning the source of the chemical energy and the form in which it is made available for work. Similarly, a plausible concept of the working machinery of muscle is emerging from contemporary studies of the contractile proteins. However, the intimate nature of the link between the two, that is, the exact manner in which the energy of the high-energy phosphate bond is applied to the work process by the contractile elements, is still largely an area for conjecture. At the moment, the most fruitful line of attack would appear to be that exemplified by this morning's essayists, who are working to complete our knowledge concerning the nature of the contractile proteins, the small molecules associated with them, and their behavior under carefully controlled conditions.

The pronounced effect of digitalis on the mechanical efficiency of the myocardium suggests that this drug may be a tool of strategic importance in studying the contractile process. Before the intimate mechanism of its action can be investigated successfully, two outstanding questions must be settled. First, the biochemical point (or points) at which it exerts its effect must be localized. Several lines of evidence suggest that digitalis influences the conversion of chemical energy to work. Conclusive proof, however, is not yet at hand. Next, it is necessary to know what chemical entities are actually responsible for the observed effect. In other words, is the biological action due to the glycoside *per se* (or a metabolite thereof), or is it the consequence of a structural resemblance between the glycoside and a chemical agent native to heart muscle? If the latter is the correct alternative, it should be possible using currently available techniques to demonstrate the presence of a digitalis-like factor in heart muscle. We are at present examining this question.

Assuming that the foregoing problems have been resolved in one way or another, it may be permissible to speculate briefly concerning the direction in which an answer to the final question may be sought. Of the various factors known to influence the activity of biological systems, that of specific ionic concentration would appear to be the most plausible one through which digitalis might operate, perhaps through a membrane effect. Finally, it may not be amiss to point out that the final solution to the digitalis problem may be materially hastened by studying the physiological function of the glycoside in the plant in which it occurs, since we now know that over a wide range of living forms many fundamentally similar problems have been solved in essentially similar ways.

REGULATORY MECHANISMS RELATING TO BLOOD VOLUME

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SCHEMATICALLY, one can compare the blood circulation with a closed pumping system, with elastic channels and a pressure pump which subsequently is filled by pressure on the pump's filling side. In such a pumping system there is an optimal relationship between the maximal velocity of the flow, the resistance and the capacity of the channel system, the liquid volume and the capacity of the pump itself. If the channel system is dilated, without the liquid volume being increased to a corresponding degree, the pressure on the filling side of the pump diminishes and thereby the filling rate also decreases. A reduction of the liquid volume has naturally the same effect. An increase of the fluid volume produces improved conditions for filling the pump, but this effect can only be made use of, if the pump's capacity is increased. An increase in the pump's capacity does not augment the effect of the system, unless the fluid volume and thereby the filling pressure of the pump, is also increased. It might seem futile to compare the circulation, which seems so complicated with its many regulatory mechanisms, with a simple pump system. However, this comparison has been found to elucidate some basic regulations of importance for an understanding of the circulation.

The peripheral part of the vascular system is adapted to the metabolically active tissue mass. Each tissue entity is provided with one or more capillaries; and as the tissue grows, the peripheral vascular system increases in direct relation thereto. Different skeletal muscles, which are used to a different degree show, however, much different capillary density; and in investigations on rats, it has been found that with physical training, there is an increase in the capillary density of the skeletal muscles, as well as of the heart musculature.[1,2] It looks, therefore, at least in reference to the skeletal and heart musculature, as if the peripheral blood vessel network is adapted to the metabolic rate. The blood conducting vessels appear to be adapted to the peripheral vascular bed, and their plasticity which can be observed under pathological conditions and in congenital defects, makes it probable that this part of the vascular system is adapted both to the tissue mass supplied and the functional demands.

Blood volume shows a direct relationship to body weight during development (Fig. 1). After maturity, the blood volume remains unaltered in humans, practically up to old age, in spite of the fact that the body weight increases in consequence of an increase in fat deposit. As a result thereof, the correlation of blood volume to body weight is low in adults. The same relationship can be observed in rats.[5] This relationship indicates that blood volume is well correlated with lean body mass, or rather, to the metabolically active tissue. The difference between the sexes as regards blood volume, would practically disappear, if the blood volume was correlated to lean body mass.

The blood volume does not appear, however, to be correlated with the metabolically active tissue mass in any simple fashion. If different kinds of animals are compared, it is obvious that the blood volume per unit body weight, varies to a great degree: for example, if rabbits are compared with cats or dogs, or sheep with men. Davis and Brewer[2] have also found that the blood volume increases in dogs during physical training. The blood volume in relation to body weight, body length, or calculated basal metabolism, has also been found to be essentially greater in athletes of both sexes, such as cross-country skiers, middle distance runners, cyclists, than in average subjects. In all, determinations have been done in my laboratory on about eighty athletes and the average differences found, are so large that they appear to exclude every doubt.

With physical inactivity it appears that the blood volume diminishes. Deitrick et al[3] found a lesser difference during immobilization, the determinations being done with Evans' blue dye. In a patient suffering from a fractured leg I have found a 15 per cent decrease. In pulmonary tuberculosis which predisposes to decreased physical activity, the blood volume is also less than

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normal, according to several investigations. During convalescence from different sicknesses, an increase in blood volume has also been found.[11,14] The blood volume accordingly appears to be unaltered or is decreased, but never becomes greater than before the administration of the drug, in spite of the fact that the stroke volume can vary essentially under these conditions. Even

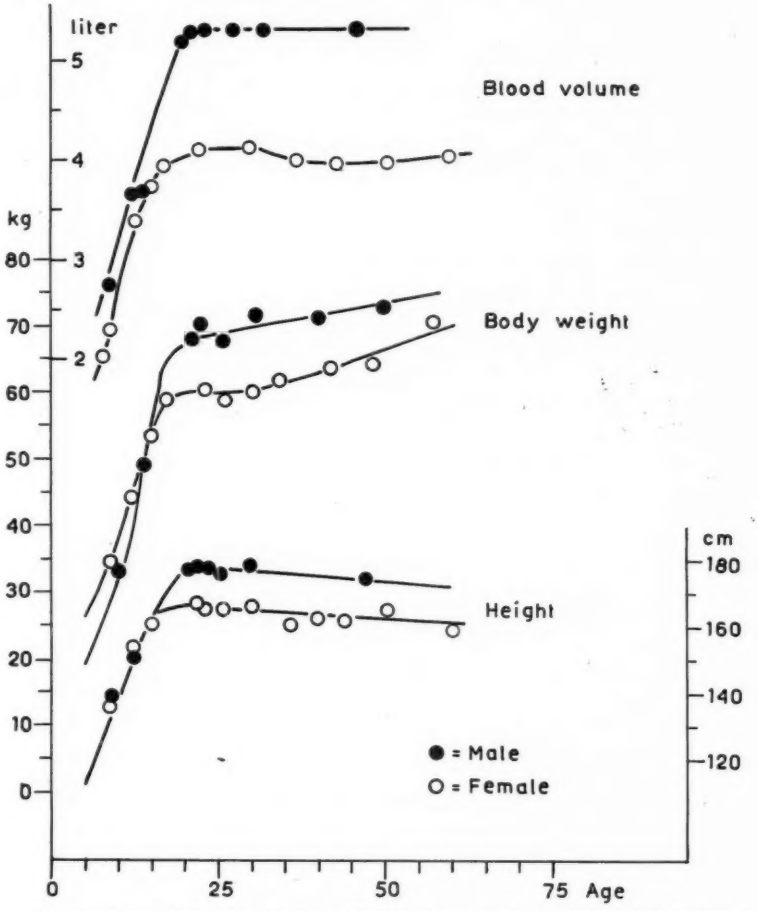

Fig. 1. The relationship between blood volume, body weight, and height and age, respectively. Each dot is a mean of determinations on at least ten different subjects.

adapted, on the one hand, to the metabolically active tissue mass, but also, on the other hand, to the metabolic rate.

The heart volume is greater when lying down than when standing or sitting, according to several x-ray investigations. The heart volume has been measured by x-ray photography in two perpendicular planes at the end of diastole, in the lying position, before, during and after, the effect of drugs like adrenalin, noradrenalin, atropin, nitroglycerin, digitalis in toxic doses: and it has been found that the heart volume remains during arduous work on the cycle ergometer, the heart volume has proved to be somewhat less than, or the same as, in the lying position.[9] Consequently under the optimal conditions for heart filling, as exist in recumbency, the heart appears to be filled maximally with blood during diastole.

The heart volume has been shown to be directly correlated with body weight. During the years of growth the correlation is very high,[10] but thereafter lower.[8] After puberty, one finds a corresponding difference between the sexes as regards the blood volume, if one correlates the

heart volume with body weight or body surface area. As is well known in physical training the heart volume increases. These variations in heart volume are conditioned, above all, by changes in the heart blood volume. The heart volume measured during life on material from men, women and athletes, respectively, has been compared with the anatomical measurement of the heart muscle volume on comparable material reported by anatomists (Fig. 2). It seems obvious from these relations, that the differences in heart volume are due chiefly to increase in the blood volume of the heart and to a minor extent to an increase in the heart muscle mass. It appears that the average thickness of the heart wall is fairly constant. The variations of heart volume with sex or physical training, appear therefore to correspond chiefly to an increase in the diastolic filling volume of the heart.

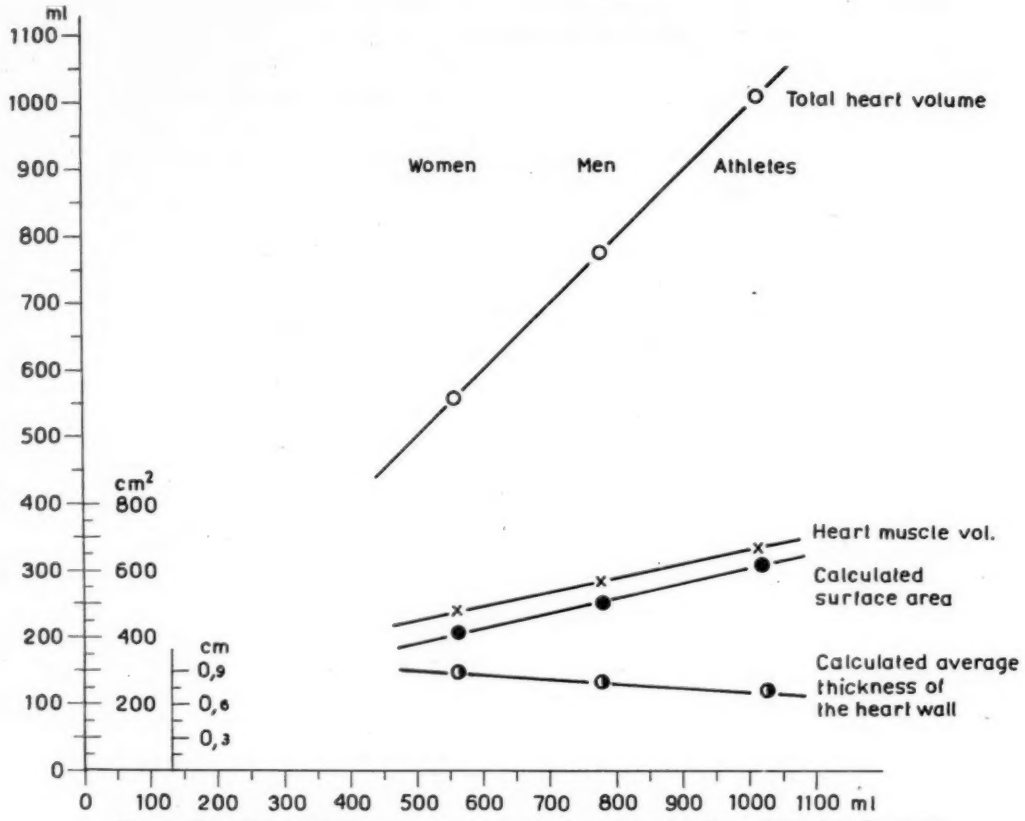

Fig. 2. The relationship between, on the one hand, total heart volume determined by x-ray during recumbency, on material composed of women, men and well-trained athletes, respectively; and on the other hand, the heart muscle volume determined postmortem on comparable material.

Now how are the capacity of the vascular system, the blood volume and the filling volume of the heart in recumbency, related to each other? By correlating the blood and heart volumes with each other, it is possible to gain an understanding of the relationship between these and the vascular system. It has been shown that there is to be found a linear correlation between blood volume and heart volume on a material from men, women and children.[8] Even in a material derived from men exclusively, but including athletes of different types, the same relation is present. Figure 3 shows the mean value for material derived from children, women, sportswomen, pregnant women; cases with pulmonary tuberculosis; average material from male subjects; and athletes of two categories, according to the degree of physical training. The values for these groups lie along one and the same regression line which

shows that there is a very close adaptation of the heart's filling volume in recumbency to blood volume and capacity of the vascular system.

How are the heart's filling volume and the blood volume related to the heart's maximal pumping effect? Adult men and women, who are made to perform work during three to five minutes on the cycle ergometer, or the treadmill until full fatigue, attain a maximum pulse rate of 190 to 200 beats per minute. Men and women attain about the same maximal pulse rate. Children reach somewhat higher values than adults, while, on the other hand, older individuals show somewhat lower values. The differences are, as a matter of fact, comparatively small. This means that the difference between individuals, in relation to the heart's maximal minute volume during work, is, for the main part, determined by the difference in the heart's maximum stroke volume. Whereas, the cardiac output increases in linear relation to the degree of the work, the pulse frequency during work stands in inverse relation to the stroke volume, and work with a pulse freqency of, for instance 170 per minute, can therefore be made use of as a relative measure of the maximum stroke volume. This work-measure is directly correlated to heart volume in the lying position and blood volume, respectively. Fig. 4 shows the correlation between work with a pulse of 170 and heart volume in material from ordinary men and women and athletes. The greater heart volume in men as compared with women, in the physically trained, as compared with the untrained, corresponds thus to the greater work performance per pulse beat. The same has been found for the relationship between the work pulse rate and the total blood hemoglobin in a material from men, including athletes, women and children.[9] There exists even a direct correlation between the blood volume

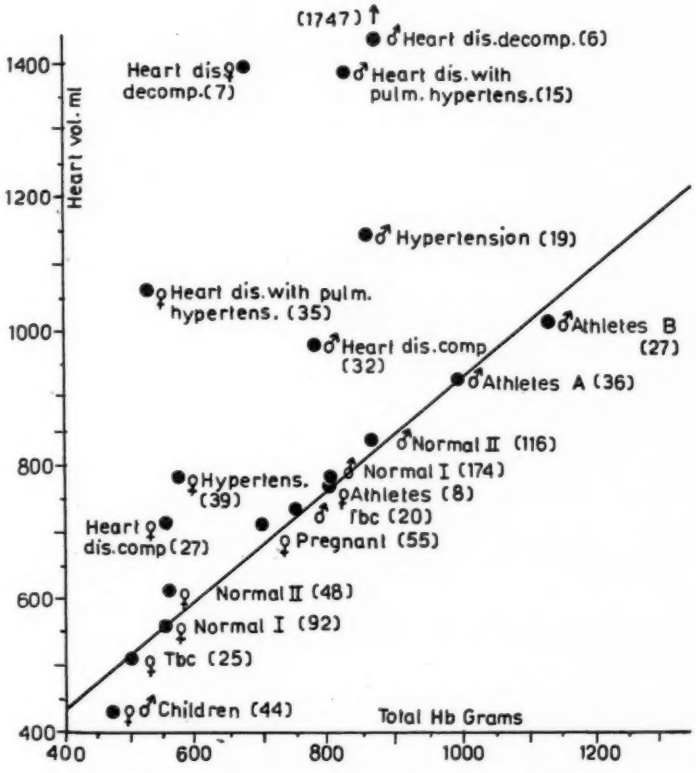

Fig. 3. The correlation between the heart volume determined by x-ray, with the subject lying down, and the total blood hemoglobin. The number of observations in each group is shown by the figure within parentheses.

and the maximal oxygen intake during exercise of short duration.[1]

Thus the maximal blood flow seems to be directly dependent upon the blood volume and tation, by way of the nervous and hormonal regulation. The latter regulation may adapt the capacity of the vascular system but may also influence the regulation of the blood volume.

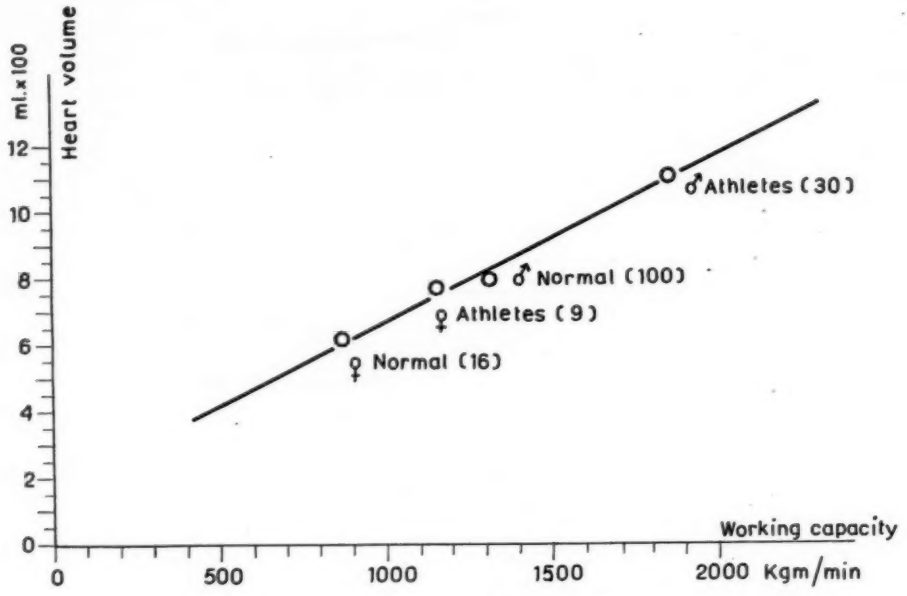

Fig. 4. The correlation between heart volume determined by x-ray and the work performance at pulse frequency 170 on average materials of women and men and well-trained athletes, respectively.

the maximal filling volume of the heart. Under normal conditions these factors are adapted to each other and to the capacity of the vascular system.

It has also been shown that between the pulse frequency at rest and at submaximal work, respectively, on the one hand, and the heart and blood volume on the other, there is an inverse linear relation.[8,9] This implies that the greater the maximum stroke volume, the greater the stroke volume at any given cardiac output, independent of whether the body is at rest or performing physical work. This implies also that the stroke volume is regulated in relation to the blood volume and the capacity of the vascular system.[13]

What regulatory mechanisms can be supposed to take part in this adaptation of the vascular system, blood volume, and the filling volume and stroke volume of the heart? One can distinguish between a morphological adaptation, of the vessel wall, peripheral vessels' density, hematopoietic tissue, and heart muscle, and a functional adap-

The most important primary control of the blood volume seems to occur by way of the water interchange between the extracellular space and the blood, which among other things, is proved by the fact that the blood volume after a hemorrhage is restored up to 90 per cent of the original amount in a short time. The mechanism in this case is probably, in broad outline, the following: as a result of the decrease in blood volume, the relationship between the capacity of the vascular system, blood volume, diastolic filling volume of the heart and stroke volume is disturbed; the blood volume on the filling side of the right and left heart is diminished and under unchanged conditions, even the stroke and minute volumes of the heart. These changes would initially evoke a decrease in the aortic pressure. This causes a change in vegetative control, in the sympathetic direction, which effects an increase in pulse rate and of vasomotor tone on the arterial side. The aortic pressure increases. As a consequence, the regulatory reflexes

on the arterial side may not be responsible for the maintenance of the new equilibrium, and for the subsequent restoration of the original circulatory equilibrium. The stimulation for these regulatory changes may be found in the peripheral and venous parts of the circulation.

Because of the decrease in central venous pressure, coincident with the increased arterial vasomotor tone, the hydrostatic pressure falls in the peripheral vessels, which in turn causes a change in the relationship between filtration and reabsorption of water in the capillaries and so reabsorption increases. Through this the relationship tends to revert to the original state of equilibrium.

The increase in vasomotor tone on the arterial side, involves in itself only an insignificant diminution of the capacity of the vascular system, and causes a reduction of total blood flow in the body. During the first phase after a hemorrhage the adaptation of the circulation is therefore markedly depressed and there is danger of insufficiency. The dilution of the blood secondary to increased vasomotor tone, has essentially a greater importance in the restoration of the circulatory equilibrium than has the direct decrease in the capacity. If this mechanism is inhibited from functioning in consequence of an alteration of vasomotor control, centrally or peripherally, or of an alteration of the water balance, a moderate blood loss may lead to a circulatory insufficiency.

A regulation in the opposite direction has been demonstrated by investigations of Fretheim[4] on the effect of preoperative blood transfusions. If blood is given in a moderate anemia, a shift of water from the blood to the extracellular space takes place and probably secondary to this, diuresis increases. The plasma volume diminishes parallel with the increase in blood cell volume. The total blood volume remains constant. With more pronounced anemias the blood volume can even diminish through transfusion, as Fretheim observed, which is explained by the fact that the capacity of the vascular system is influenced by the oxygen concentration of the blood.

With a primary increase in the capacity of the vascular bed such as occurs during pregnancy, the heart volume as well as the blood volume increase, the latter in some cases alone, through an increase of the plasma volume.

In heart disease, the normal relationships between blood volume, heart filling volume and stroke volume are changed, often to a very great degree. The blood volume has been determined in 270 heart cases, with a well-established diagnosis, and where the circulatory relationships in most cases were analysed by means of cardiac catheterization. It was found, that in cases without stasis in the pulmonary or systemic circulations, but with a slight or moderate heart enlargement, the blood volume was lower than normal, which might be related to physical inactivity which the heart disease forces upon these cases. Heart patients who have stasis in the lesser circulation, and who on the average, had somewhat low minute volume values, showed a small increase of blood volume, especially in men. Cases with increased venous pressure in the systemic circulation, showed in the female subjects, a still more pronounced increase of blood volume. However, the greatest blood volume was found in cases of congenital heart disease with polycythemia, which cases as a rule have neither stasis nor diminished cardiac output. The vascular system can be expected to have become adapted in these cases to the altered circulatory relationships, particularly with regard to the reduction of the arterial oxygen saturation.

In heart disease, the heart volume varies to a much greater extent than the blood volume and the relation between blood and heart volumes is changed which is evident from Fig. 3. One can also show that the relationship between heart filling volume and blood volume, on the one hand, and pulse frequency during work on the other, also departs from the normal to a marked degree.

This condition of things makes possible a more exact basis for the use of the radiological determination of heart volume,[6,7] and for testing the physical working capacity which has been used in cardiological practice during the last three years. Such an analysis has been found to be of definite value, as much in establishing a diagnosis, as in evaluating different cardiac symptoms from the functional point of view.

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(Continued on Page 29)

VENOMOTOR TONE AND BLOOD VOLUME CONTROL

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IN THE PRECEDING paper by Dr. Torgny Sjöstrand, the author has presented a small portion of his comprehensive work concerned with the quantitative assessment of the relationships between blood volume on one hand and sex, geometry and activity of the body on the other hand. From his detailed measurements related to the distribution of blood volume,[11] he pointed to the fact that the size of the heart, particularly the diastolic volume, is an aliquot portion of the blood volume. The interesting observation that the heart rate at a given work output can be predicted from the available blood volume suggests that hemostatic parameters form the base on which possible response patterns of hemodynamics are laid out. In the following I want to present some of our own work, together with Dr. J. P. Henry, Dr. H. O. Siker, Dr. W. E. Wendt and Dr. J. L. Reeves, on blood volume control which throws light from a different angle on issues raised by Dr Sjöstrand.

The close relationship of blood volume to geometry and activity of the body calls for the existence of a blood volume regulatory mechanism which continuously adjusts the blood volume to the size of the vascular bed and the activity of the body. Because the size of the vascular bed depends on the state of contraction of the vascular walls, one must anticipate also a close interplay between control of blood volume and control of venomotor tone. Since von Goltz showed that the blood volume is much too small for the potential capacity of the vascular bed, many investigations have been directed towards the clarification of the mechanisms which control the tension of the blood vessels. It was, thereby, always assumed that the blood volume was constant. This assumption is not justified. During modest blood volume changes induced by hemorrhage or blood transfusions the low pressure system, in contrast to the arterial system, does not aim for constancy of pressure. When, for instance, 500 cc. of blood was drawn or infused at a rate of 300 cc. per minute, the central venous pressure varied linearly by approximately 7 cm. water per 1000 cc. Except for transient initial disturbances rapid transfusions followed the same course. There was from subject to subject surprisingly little scatter, indicating, that vascular tone of the low pressure system, as expressed by $\frac{\Delta P}{\Delta V}$ is in the normal man under resting conditions a rather constant biological parameter. Regardless of the initial rate of blood volume change, the venous pressure only very gradually returned to normal witin 3 to 4 hours.[2,4] The persistence of the hemostatic unbalance induced by blood volume changes is remarkable for two reasons. It may furnish a long lasting stimulus, influencing the dynamics of the arterial system and thereby be responsible for the peculiar behaviour of heart rate described by Dr. Sjöstrand, which would be difficult to explain on grounds of the carotid sinus receptors alone. Another even more important question is this: Does the long persistent change of pressure and volume in the low pressure system represent the adequate stim-

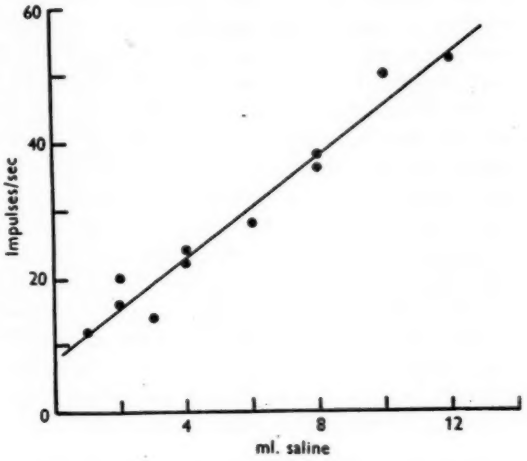

Fig. 1. Paintal: Relation of frequency of discharge in a type B left atrial fibre to various levels of atrial filling in an isolated left atrium.

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Presented in the Symposium on Recent Advances in Cardiovascular Physiology and Surgery, University of Minnesota, Minneapolis, September 14, 1953.

ulus for a volume regulatory mechanism which restores the physiological balance, not by changing the tension of the vascular walls, but by restoring the volume to normal?

or the arterial hemodynamics. It is irrelevant whether the volume increase is induced by a blood transfusion,[1] plasma transfusion,[13] or the injection of washed red cells.[12] If the concept is

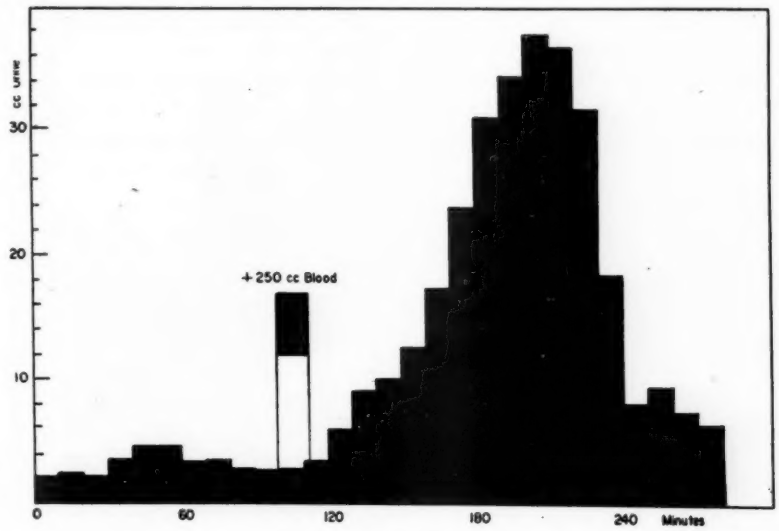

Fig. 2. Effect of a blood transfusion on urine flow in a chloralosed dog. 250 cc. of blood were infused during a period of 15 minutes.

Such a mechanism presupposes the existence of volume sensing elements either in the total circulation, or in parts of the circulation where the distensibilities are representative of the distensibility of the total circulation. While little is known about stretch receptors in the peripheral circulation, a whole variety of such elements has been described in both auricles by Nonidez.[8] Recently Paintal[9] has clearly demonstrated that the vagus carries centripetal impulses which are related to the degree of distention of the auricles rather than the pressures (Fig. 1).

Looking for an indicator organ, for a volume regulatory reflex, one has to keep in mind that final adjustments of blood volume comprise effects on blood protein formation, blood cell volume and water balance. While the first two are rather inaccessible, the excretory part of water balance could with proper precautions be used. One should expect an increase of water excretion with blood transfusion and an oliguria with hemorrhage. Figure 2 is an example of a diuresis produced by a blood transfusion which cannot be attributed to changes of the osmotic conditions

true, that this effect of blood volume changes on water balance is initiated by Nonidez receptors, and probably executed through the ADH mechanism, the signals being carried to the center in the vagus, it should be possible to obtain the same response of the kidney by a local distention of the circulatory organs which have stretch receptors intercalated in their walls. A slight engorgement of both auricles along with the pulmonary circulation can easily be achieved in lightly anesthetized dogs and normal humans by application of 5 to 15 cm. water constant negative pressure breathing. This procedure leads to an increased urine flow of the type of a water diuresis[5,10] (Fig. 3). Considerable strength has been added to the arguments in favor of the proposed volume regulatory mechanism by the following two observations. In dogs, the effect of negative pressure breathing on urine flow could be eliminated by vagus block.[3] Furthermore, acute inflation of a cherry size balloon, suspended in the left auricle was accompanied by a dramatic diuresis which subsided promptly on deflation of the balloon.[7] This procedure was accompanied by no change or a slight

decrease of arterial pressure and an increase of left auricular and pulmonary arterial pressures of approximately 5 to 10 cm. water.

The latter results are at variance with those of

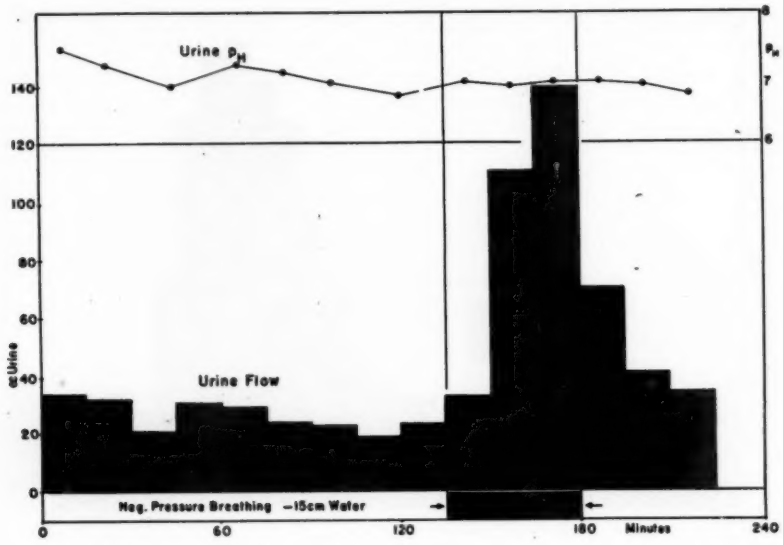

Fig. 3. Sieker et al: Effect on urine flow in humans of 15 cm. constant negative pressure breathing. Negative pressure breathing was applied for 45 minutes (heavy black band on bottom of chart).

Hamilton,[6] who found retention of sodium and edema formation in dogs with induced chronic mitral stenosis. In this respect it is interesting to note, that in a normal subject all physiological events which produce a decreased filling of the thoracic pulmonary organs are accompanied by oliguria, while increased filling of the thoracic circulatory organs are usually accompanied by diuresis.[10] The great exception to this rule being congestive heart failure, tentatively leads to the working hypothesis that certain forms of edema formation may be caused by a perversion of the described hemostatic reflex for the control of blood volume.

Both this work and that of Dr. Sjöstrand converge in the emphasis of herostatics as a basic part of the functional structure of the circulation.

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HEART SIZE AND STROKE VOLUME

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IN RECENT YEARS, the traditional descriptions of cardiac function and control have been found inadequate for explaining many experimental and clinical observations. Commonly the heart's response has been predicted from two basic concepts: (a) that the diastolic volume is determined by the effective filling pressure,[31] and (b) that increased initial length of myocardial fibers (greater diastolic volume) causes increased energy release during the next contraction.[16] In other words, the typical ventricular response to a greater pressure, or volume load, is generally described as an increase in diastolic volume. The inevitability of this response is being questioned more and more frequently. Wiggers[28] recently emphasized that Starling's law of the heart applies only "under equal states of responsiveness" of the myocardium since the physiological state of the myocardium is changed by coronary blood supply, humoral agents and nervous actions.

The basic principles of cardiac function were originally based on cardiometer and pressure records obtained from the hearts of anesthetized, thoracotomized dogs. Controlled experiments of this type indicate the capabilities of the heart, i. e., what the heart can do under these particular experimental conditions, but they do not necessarily delineate how it responds under normal conditions. To apply these experimental results directly to normal cardiac function is to imply that the heart behaves in the same way in both normal and abnormal conditions. Obviously this is not so for many reasons, including: (a) Anesthesia unquestionably depresses neural controlling mechanisms. (b) Induced experimental loads are not the same as circulatory adjustments to normal activity; for example, increasing the volume load by elevating a reservoir of blood does not necessarily reproduce the normal adaptations to exertion. (c) Thoracotomy, as we have recently demonstrated, is generally associated with a striking reduction in heart size.[21] A typical example of this response is illustrated by the tracings in Fig. 1. The area of the cardiac silhouette diminished strikingly even before the heart itself was manipulated and the reduced size persisted in this

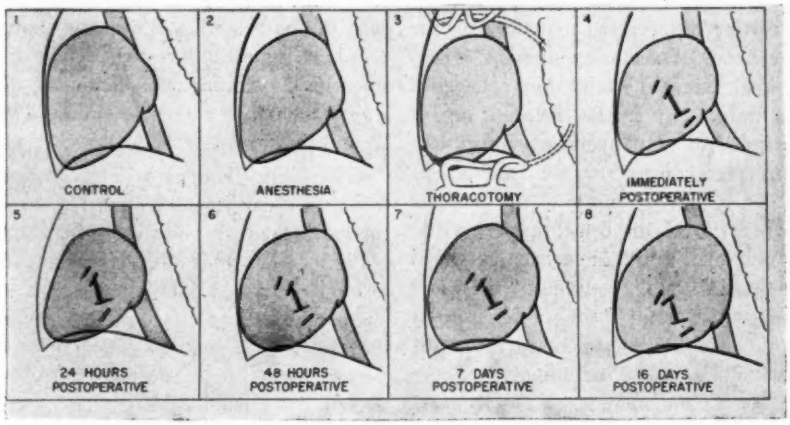

Fig. 1. Tracings of the cardiac silhouette from roentgenograms taken before, during and after thoracotomy, indicate the extent to which the heart becomes smaller when the thorax is opened. Diminished heart size persisted for more than twenty-four hours in this case, and the changes in left ventricular diameter were recorded after forty-eight hours.

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instance more than twenty-four hours after the thorax had been repaired. Changes in the left ventricular area were recorded by cinefluorographic angiocardiography. When the chest was open, the left ventricle emptied almost completely during systole, but considerable quantities of blood remained at the end of systole when the thorax was intact. If the ventricles were abnormally small at the beginning of the original cardiometer measurements, greater diastolic expansion might occur because the ventricles could not get any smaller.

In the previous presentation, Dr. Sjöstrand[27] made the interesting observation that the diastolic volume of the heart of reclining humans is apparently maximal, since he and his colleagues were unable to induce any further increase in size by various drugs and maneuvers which should, according to accepted concepts, cause diastolic expansion. Relatively large volumes of residual blood in the heart of both intact experimental animals[21,23,25] and man[1,9,10,14] have been reported as has a reduction in systolic volume of the heart during exercise.[11,13] Most of these studies utilized roentgenographic techniques which do not indicate the size or volume of the individual chambers of the heart. Thus, the changes in total heart volume represent variations in the volume of any or all of the cardiac chambers. Since the atria, and right and left ventricles, differ widely in their anatomy, geometry, functional architecture and operating conditions,[22] they must be studied individually, not collectively. No method is available at present for measuring directly the absolute volume in a cardiac chamber, but a technique has been devised for continuously measuring the diameter of the left ventricular chamber in the intact unanesthetized dog.[20]

Measurements of Left Ventricular Diameter in Unanesthetized Dogs

The left ventricular diameter was recorded from variable inductance gauges, consisting of a coil 3 mm. x 15 mm., anchored to the free wall of the left ventricle, and a magnetic steel stylus anchored at one end to the interventricular septum (Fig. 2B). The gauge was installed within the ventricle under aseptic conditions by means of trochars.[20] When the ventricular walls contracted and relaxed, the stylus moved in and out of the coil. Delicate wires from the coil extended through the heart wall, between pulmonary lobes, and through the thoracic wall to the outside. The variations in inductance were continuously recorded to determine the position of the stylus within the coil. Since the thorax was open when the intraventricular gauges were installed, the very small left ventricle would barely admit the coil (Fig. 1), and the stylus was immobilized within the coil throughout the cardiac cycle. After twenty-four to twenty-eight hours, the heart had expanded to approximately preoperative size. (The marked reduction in heart size noted during operation on these dogs is in line with our previous contention that thoracotomy induces shrinkage of the heart.[21]) When the animal had recovered, changes in left ventricular diameter were measured continuously during all manner of activity including rather strenuous exertion (Figs. 2 and 3).

The cyclic changes in left ventricular diameter resembled cardiometer records except for a sharp upward deflection during isometric contraction (Fig. 3A). This deflection apparently represented a sudden increase in diameter due to a change in shape of the ventricles without a change in volume. The "end diastolic" diameter was measured at the peak of the A wave (Fig. 3A), which was produced by atrial contraction. The diastolic diameter ranged around 25 mm. The change in diameter during systole amounted to only 3 to 5 mm. which affirms the presence of relatively large volumes of residual blood within the ventricle.

The Startle Response:—The immediate response to an unexpected loud noise was a transient increase in both systolic and diastolic diameter, often followed by a sustained increase in diastolic and stroke diameters (Fig. 3C). The initial increase in diameter and the accompanying tachycardia began during the first cycle after the stimulus (Fig. 3C). We have interpreted these prompt changes in heart size and heart rate as due to neural reflexes acting directly on the heart and circulation.

The Cardiac Response to Exercise:—The first change in cardiac function during exercise was a prompt acceleration of the heart rate, and a progressive reduction in the diastolic and systolic diameters. These changes usually began immediately after the onset of the exercise, but sometimes began in anticipation of the exertion. After

a few seconds, the heart rate slowed and the diastolic diameter returned to approximately the pre-exercise level while the systolic diameter usually remained smaller. Systolic ejection during exercise was generally beyond the recording range of the gauge, which blocked during every systolic interval. For this reason, it was impossible to ascertain the extent of the systolic deflection. After the exercise, both the systolic and diastolic diameters generally increased beyond and then returned to the control level. The absolute diameter changed less than was anticipated. However, relatively large changes in the volume ejected can result from small differences in the degree of filling or ejection when the ventricle operates at large dimensions. The fact that the diastolic diameters increased during startle and after exercise indicates that the ventricles were not operating at maximum diastolic volumes during the control period or during exercise. The diastolic diameter increased during a startle reaction and decreased at the onset of exercise even though tachycardia was present on both occasions. Thus, the heart rate is not the principal factor affecting left ventricular diameter.

These experiments represent merely the first step along an arduous path toward describing cardiac function and control in intact animals. Thus far, gauges have been successfully installed in fourteen animals. The response to exertion has been recorded forty times in four animals. Although the details of the response vary during exertion or startle, even in the same dog, the general patterns appear to be consistent. Nonetheless, data are still insufficient to derive principles of cardiac function which could be applied with confidence to other dogs or to man.

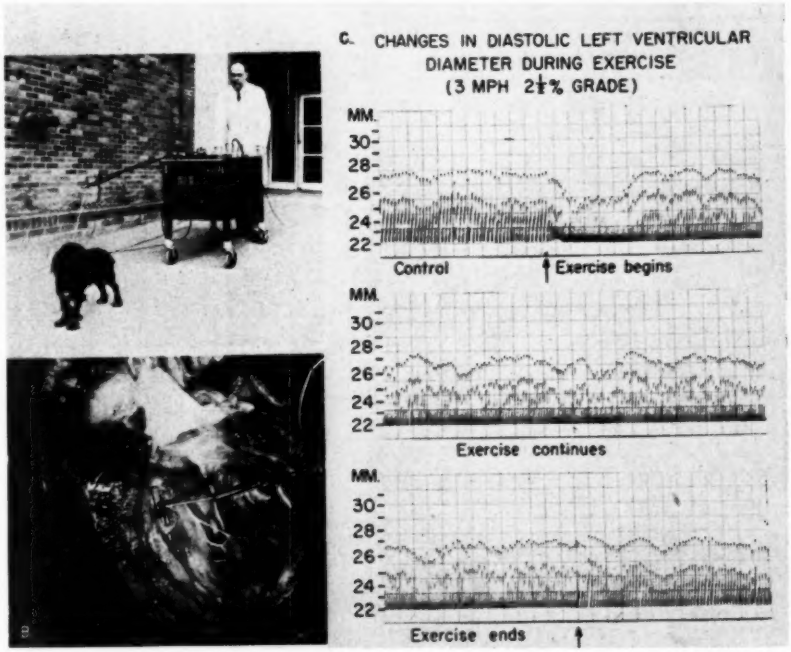

Fig. 2. (A) After recovery from the operation, dogs were exercised while running freely on a treadmill. (B) The variable inductance gauge, consisting of a coil and stylus, which recorded the changes in left ventricular diameter. (C) The initial response, to exercise on a treadmill, was a precipitous reduction in both diastolic and systolic diameters, as the heart rate accelerated. The gauge blocked with each systolic excursion during exercise indicating that the systolic diameter was less than during the control period.

The Systolic and Diastolic Reserve Volumes

In the current experiments, the cardiac response to voluntary exertion is significantly different from the changes induced by increased venous return to exposed hearts enclosed within a cardiometer as illustrated schematically in Fig.

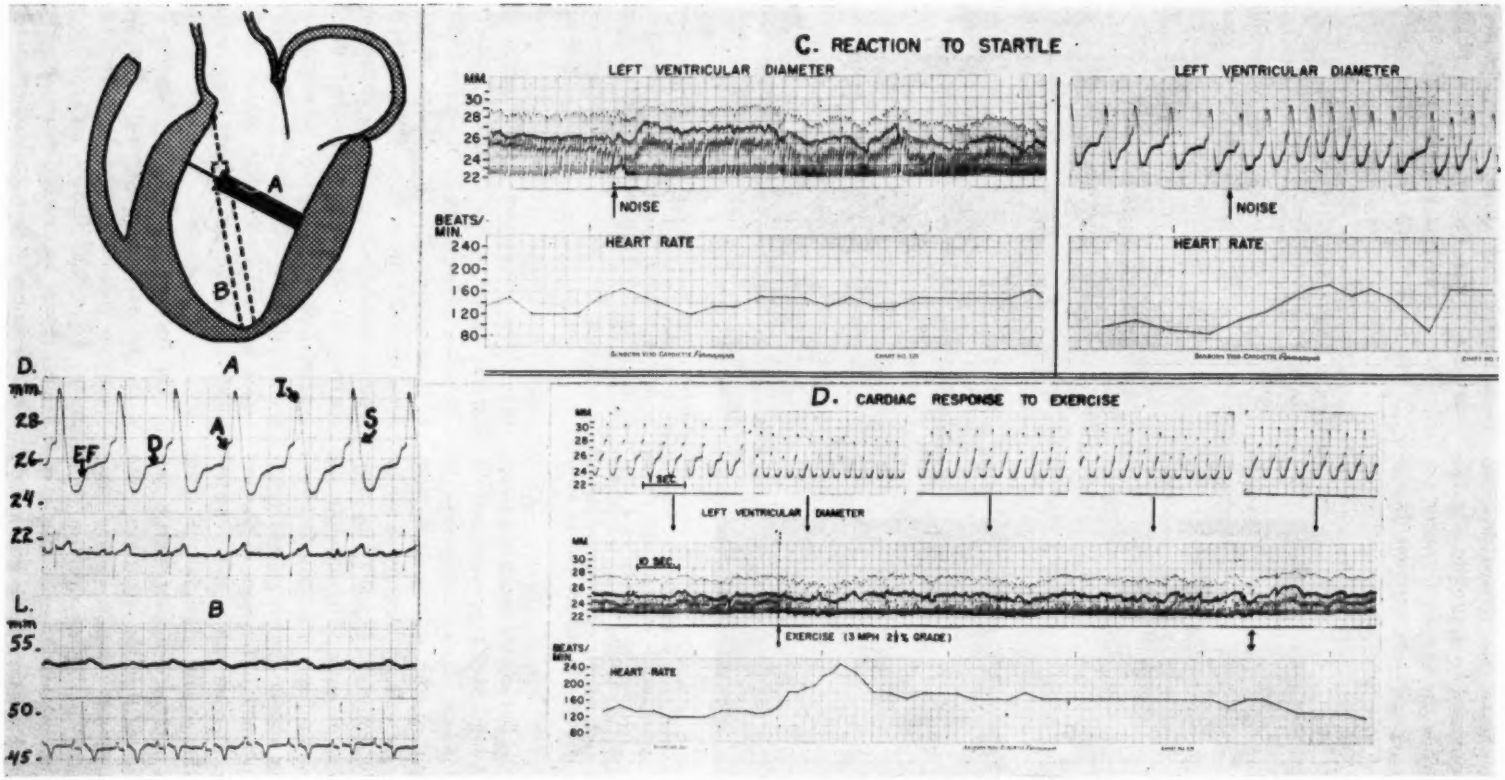

Fig. 3. (A) The changes in left ventricular diameter during each cycle consist of five phases: (EF) early filling, (D) slow filling or diastasis, (A) auricular filling, (I) isometric expansion of the diameter, and (S) systolic ejection. (B) The length of the chamber from the root of the aorta to the apex changes very little during each cycle, but the axis from the apex to the mitral valve ring shortens significantly on cinefluorographic films. (C) The response to startle is illustrated using slow paper speed (2.5 mm./sec.) on the left and the initial effects with fast paper speed (25 mm./sec.) on the right. (D) The changes in left ventricular diameter and heart rate are shown in these sample records. The end diastolic diameters at the peak of the A waves are connected by a continuous line.

4. The increase in stroke volume during exercise is usually attributed to increased venous return, and increased central venous pressure producing greater diastolic distention. The current studies indicate that under resting conditions, the left ventricle is not fully distended during diastole, and is far from being completely emptied during systole. Stroke volume may be increased by more complete systolic ejection or by greater diastolic distention. For convenience, we suggest that the term "systolic reserve volume" be applied to the quantity of blood remaining in the ventricle at the end of a normal systolic ejection at rest. Similarly, the additional quantity of blood which could be accepted by greater diastolic filling might be labeled the "diastolic reserve volume" (Fig. 4). Increased stroke volume might be attained by encroaching on either systolic reserve or the diastolic reserve. Even with a constant stroke volume, the magnitude of the systolic and diastolic reserve volumes may be varied by changes in the "physiological" condition of the ventricular myocardium. We would limit the term "residual" blood to the small quantity of blood remaining in the ventricle after maximal systolic ejection. These terms correspond to those employed in describing lung volumes and have the same logical basis.

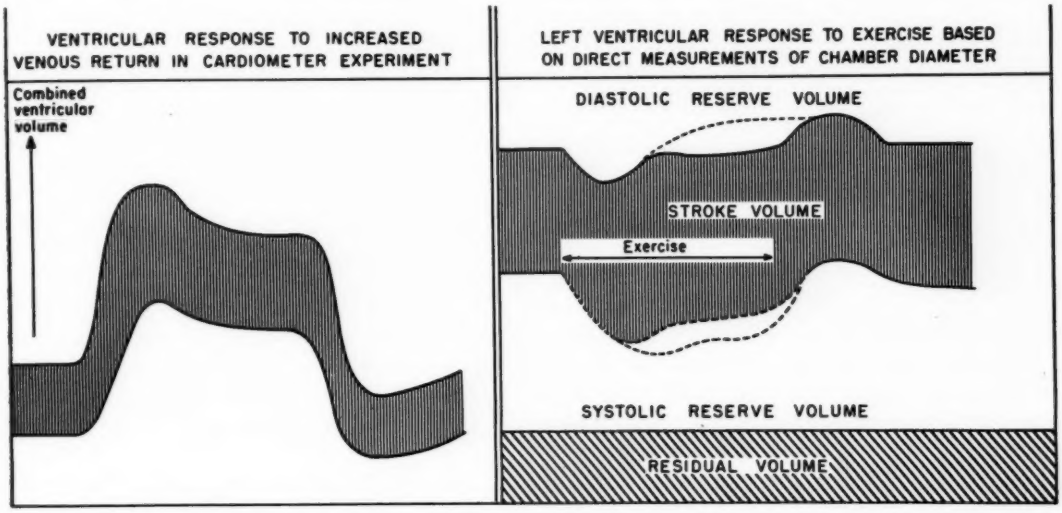
VENTRICULAR RESPONSE TO INCREASED VENOUS RETURN IN CARDIOMETER EXPERIMENT
Combined ventricular volume
LEFT VENTRICULAR RESPONSE TO EXERCISE BASED ON DIRECT MEASUREMENTS OF CHAMBER DIAMETER
DIASTOLIC RESERVE VOLUME
STROKE VOLUME
Exercise
SYSTOLIC RESERVE VOLUME
RESIDUAL VOLUME

Fig. 4. In cardiometer experiments, the diastolic volume, stroke volume, and systolic volumes are all increased during increased venous return (after Patterson, Piper and Starling[16]). According to the author's concept, the stroke volume of the left ventricle is increased during exercise primarily by greater systolic ejection, encroaching upon the systolic reserve volume. By utilizing both the diastolic and systolic reserve volumes (dotted lines), larger volumes of blood can be ejected during each cycle.

Since the left ventricle is neither completely filled during diastole nor completely emptied during systole, the factors which limit the expansion and contraction of the chamber must ultimately be established. In this way the mechanisms for increasing stroke volume might be approached more logically.

Factors Which May Influence Stroke Volume

Stroke volume is the quantity of blood which leaves each ventricular chamber between the end of diastole and the end of systole. Some of the factors which promote or impede diastolic distention and systolic ejection will be considered individually (Table I). Several of these are not generally considered in this regard and deserve attention even though the available evidence is inadequate to indicate their relative importance. Those items which might be directly affected by nervous or hormonal controlling mechanisms will be mentioned.

Systolic Ejection.—The ventricles eject blood into the arterial systems as long as the intraventricular pressures exceed the pressures in the roots of the corresponding arterial trunks. The intraventricular pressure is elevated by contractile tension developed by myocardial fibers within the ventricular wall. The ventricular walls are

composed of layers of myocardial bundles, intricately interwoven and oriented in different directions. The contribution of any particular myocardial fiber depends upon its contractile tension, its anatomical position and orientation within the wall, and the geometrical characteristics of the chamber itself.[22] The right ventricular cavity is a crescentic space between the concave-convex surfaces of the free wall and the interventricular septum. The right ventricular wall consists primarily of two myocardial layers which spiral in opposite directions. Simultaneous contraction of these two layers draws the base of the heart (tricuspid valve ring) toward the apex of the heart. Any movement of the right ventricular wall toward the septum produces a bellows-like action which will displace large volumes of blood per unit of myocardial shortening. In the left ventricular wall, a thick cuff of muscles lies between the two spiral layers and encircles the cavity like a clenched fist. Changes in size and shape of the two ventricles are very different during systole. Cinefluorographic angiocardiography has shown that during left ventricular contraction, the relative decrease in diameter is much greater than the relative shortening along its longitudinal axis. Until more data are available, discussion of cardiac contraction must be restricted to general terms with no attempt to analyze the contributions made by individual myocardial bundles and layers. Thus, the stroke volume is established by the amount the various layers of myocardial fibers can shorten before the effective contractile tension is insufficient to maintain an intraventricular pressure higher than arterial pressure. Since arterial pressure is maintained within a relatively narrow range during changes in the level of activity, this factor will not be considered further.

Turbulence in the arterial trunks and resistance to the flow of blood through the ventricular chambers[8] represent energy waste. Energy is dissipated in many other ways as well so that only about ten to twenty per cent of the energy released by the myocardium appears as useful work: pressure and flow of blood leaving the chambers. The energy released by the heart and total work accomplished are both expressions of myocardial "contractility."

TABLE I. FACTORS INFLUENCING STROKE VOLUME

Systolic Ejection	*Diastolic Filling*
I. Outflow Resistance	I. Effective Filling Pressure
(a) Arterial pressure	(a) Diastolic ventricular pressure
(b) Turbulence	(b) Intrathoracic pressure
II. Ventricular "Contractility"	II. Ventricular Distensibility
(a) Myocardial "contractility"	(a) Myocardial distensibility
(b) Myocardial viscosity	(b) Myocardial viscosity
(c) Law of Laplace ($P = \frac{T}{R}$)	(c) Law of Laplace ($P = \frac{T}{R}$)
(d) Interfascicular tension	(d) Interfascicular tension

Myocardial Contractility.—No definition of "contractility" has been universally accepted. For purposes of this discussion, the term will be employed to describe the degree of myocardial shortening in relation to the work accomplished. According to this definition, ventricular myocardium, under constant or increased load, displays greater "contractility" the more completely it empties the chamber during systole. In this light, it is profitable to consider some of the factors which affect contractile tension in relation to myocardial shortening.

Contractile tension of myocardium is affected by the initial length or diastolic volume of ventricles at the onset of contraction.[28] The familiar length-tension diagram describes this relationship by a single curve indicating that contractile tension increases as the fibers are stretched up to a critical level.[5] However, fiber length is only one of many factors influencing myocardial contraction. It is well known that epinephrine increases "contractility" as evidenced by greater intraventricular pressure, faster elevation of pressure, reduced duration of systole,[29] and more complete systolic ejection.[24] Sympathetic nerves, distributed throughout the ventricular walls, discharge epinephrine-like substances which apparently have the same functional effect as circulating epinephrine.[7,17,18,19,26] The rapid reduction in systolic and diastolic diameter at the onset of

exercise (Fig. 2), might well result from sympathetic discharge to the myocardial wall. Since heart rate and diameter may change in anticipation of exertion, we must not ignore the possibility that such autonomic controlling mechanisms are initiated in the higher levels of the central nervous system. It is commonly stated that tachycardia is responsible for reduced heart size. The fact that an accelerated heart rate may occur with either an increase or a decrease in left ventricular diameter (Fig. 3) suggests that these changes in size are not the direct result of shorter cycle length. It seems more likely that the factors which produce tachycardia, such as autonomic discharge, usually, but not invariably, promote increased systolic ejection by inducing increased "contractility."

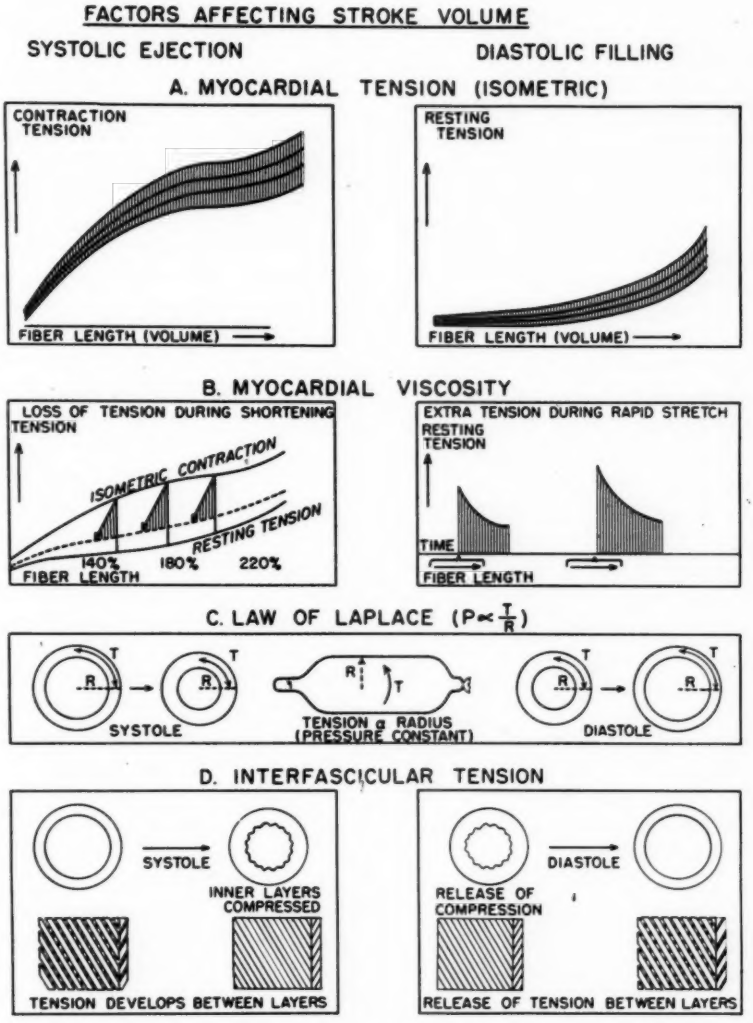

Fig. 5. Some of the factors which may influence stroke volume are schematically illustrated. Each of these factors affects both diastolic filling and systolic ejection (see text).

Thus, changes in "contractility" of the myocardium represent altered "physiological" conditions of the myocardium. Therefore, the traditional length-tension curve alone does not adequately describe "myocardial contractility." In-

stead, a family of curves must be established to indicate the range within which the musculature may operate under varying physiologic conditions of the myocardium (Fig. 5A). This will require a great deal more investigation of myocardial activity during contraction at constant length (isometric) and with myocardial shortening during contraction. The schematic length-tension diagrams in Figure 5A represent muscles contracting isometrically. However, muscular contraction without shortening can perform no external or useful work.

Myocardial viscosity is a term used by Lundin[12] to describe a pronounced drop in contractile tension which occurs when myocardial strips shorten during contraction. Viscosity effects in contracting muscles have also been observed by other investigators.[2,6] During isometric contraction, myocardial fibers develop high tension rapidly and sustain it well during their contraction. In contrast, if the muscle shortens rapidly after the peak of isometric contraction has been reached, the tension falls off abruptly even though contraction continues. The drop in tension is increased as the rate and extent of shortening increases so that with extreme shortening, contractile tension approaches resting tension. The term "viscosity," as applied to this phenomenon, indicates that the loss of tension is probably due to "friction" within the myocardial fibers as the contractile elements are rearranged during a sudden change in length. Since the ventricles cannot eject blood without shortening of the myocardial fibers, this drop in tension assumes great importance in cardiac function.

The larger the diastolic volume, the less the myocardial fibers must shorten to eject a particular volume of blood. Both the rate and extent of myocardial shortening are reduced when the ventricles contract from large diastolic volumes. The loss of energy required to overcome internal friction (myocardial viscosity) is similarly diminished by diastolic expansion. Thus, the contractile tension, and the work accomplished per unit of energy released (efficiency), are theoretically increased when diastolic volumes are large and the initial length of myocardial fibers is relatively great. If nervous or hormonal influences could reduce viscosity, this effect would be another mechanism for direct neural control of "contractility."

The Law of Laplace.—The pressure within a hollow cylinder is maintained by tension in the walls. The amount of tension required to support a particular pressure is proportional to the radius of the cylinder.[4] The relation between the pressure (P), the wall tension (T) and the radius of the cylinder (R) is expressed by the formula: $P = \frac{T}{R}$ (the law of Laplace). A partially inflated, sausage-shaped rubber balloon illustrates the principle.[32] During the initial inflation, considerable pressure is required to produce any distention. When one portion of the balloon begins to distend, further inflation is much easier. At the stage illustrated in Fig. 5C, the inflated portion has a large radius; the wall is very tense and resists indentation. The portion of the balloon with a small radius supports precisely the same pressure, but the walls are relatively flaccid and readily compressed. In this case, the pressure is constant throughout the balloon and the wall tension is directly proportional to the radius.

If the left ventricle is considered a cylinder[25] surrounded by circularly oriented fibers (the deep muscle bundles), the tension in the myocardial fibers required to sustain a particular level of intraventricular pressure is greater when the ventricle is distended than when it is more completely emptied. If all myocardial layers developed the same tension, the inner layers of myocardium would be more effective in elevating intraventricular pressure than the outer layers.[22,25] If the myocardial fibers sustained the same tension during shortening, the intraventricular pressure could rise progressively as the ventricle emptied. Actually, the tension lost during myocardial shortening is compensated to an unknown extent by the decreasing radius described by the myocardial fibers as the chamber is emptied. The spiral muscle layers in the right ventricular wall describe a circle of very great radius and would have to develop extremely high tension to produce right ventricular pressures as high as the normal left ventricular pressure.

Interfascicular Tension.—Obviously the degree of myocardial shortening is not the same in different myocardial layers. The internal circumference of the left ventricular wall is the most reduced; the outer layers of circularly arranged

fibers shorten to a less extent and the superficial spiral muscles shorten least of all. The various muscle layers are entwined and interconnected. If one layer contracts more than the other during systole, stress is applied to the connections between them.[22] This might compress the inner layers of the left ventricular wall as in Fig. 5D.[3] The various myocardial layers are oriented in different directions, schematically represented by a basket work in Fig. 5D. If the fibers in these two layers are connected together and all shorten simultaneously, tension will develop in the connections between them. These two forms of stress in the connections between muscle bundles have been termed "interfascicular tension."[22] The energy of contraction expended in placing these connections under tension is wasted so far as systolic ejection of blood is concerned. Assuming that minimal tension between layers occurs at or near the normal diastolic level, the greater the myocardial shortening, the greater the interfascicular tension. Obviously then, the lesser degree of myocardial shortening in the various layers, when the ventricles function at large diastolic dimensions, also diminishes the energy wasted in developing interfascicular tension.

Thus, the extent of systolic ejection depends upon the contractile tension which is developed and sustained by the myocardial fibers as the ventricles eject blood. Myocardial tension becomes progressively more effective in elevating the intraventricular pressure as the radius of the chamber is diminished. This beneficial effect is countered by the loss of tension during myocardial shortening due to myocardial viscosity and the energy wasted as interfascicular tension. There are undoubtedly other factors, but it is clear that the ventricles derive certain important mechanical advantages by functioning at large diastolic dimensions with relatively large quantities of systolic reserve blood. The author believes that the systolic reserve volume is normally greater than the diastolic reserve as indicated in Fig. 4. Encroachment upon the systolic reserve when the ventricles accomplish greater amounts of work requires increased myocardial "contractility."

Diastolic Filling

Ventricular filling occurs in three stages when the heart rate is sufficiently slow (Fig. 3A). A major portion of inflow occurs during the early diastolic period, beginning immediately after completion of systole. The rapid filling phase ends with a relatively abrupt transition to a period during which inflow is slow or stopped (diastasis). Finally, a variable increment of blood enters the ventricle during atrial systole just before the succeeding ventricular contraction. Since space is limited, the discussion will be largely restricted to the factors which affect ventricular filling during early diastole. The volume of blood in the ventricles during diastole is determined by two principal factors: (a) The effective filling pressure and (b) the resistance to distension offered by the ventricular walls (Table I). The rate of filling is determined by the atrioventricular pressure gradient and the resistance to distension. The "effective" filling pressure refers to the combined action of intraventricular pressure and the distending influence of the subatmospheric intrathoracic pressure. If the pressure within the ventricles and central veins and the fluctuating intrathoracic pressure are considered to remain within fairly narrow limits, ventricular resistance to stretch (distensibility) is the principal limiting factor to be discussed. Distensibility is defined as the diastolic ventricular volume per unit of effective filling pressure. If the ventricle accepts a greater quantity of blood without an increase in effective filling pressure, the distensibility is increased.

Myocardial Distensibility.—When relaxed myocardium is progressively stretched, the resting tension increases, gradually at first and more rapidly as the elongation continues. The relation between resting length and resting tension was illustrated by Frank[5] as a single curve, which implies that the diastolic volume is determined by the diastolic filling pressure (e.g. distensibility is constant). Actually there is direct evidence that epinephrine increases ventricular distensibility,[15,17,24,29] summarized by Wiggers[29] as follows:

> "Restated, the diastolic volumes of the ventricles can be increased beyond their normal capacity (1) by an increase in initial pressure overcoming the inherent tendency of the ventricles to resist stretching or (2) by a reduction in this inherent power of the ventricles to resist stretching, i.e., by a reduction in their tonus. Under normal conditions the former mechanism operates; under epinephrine the latter mechanism not only enters, but predominates."

A similar conclusion was derived from measurements of left ventricular area and effective filling pressure in intact, anesthetized dogs.[24] If

the diastolic volume increases without a corresponding increase in effective filling pressure, the length-tension relationship for resting myocardium must be represented by a family of curves or a range within which the myocardium functions under varying physiological states. These observations indicate that circulating epinephrine or sympathetic discharge releasing epinephrine-like substances within the ventricular walls can increase both myocardial distensibility and contractility to provide greater stroke volume by both greater diastolic filling (without increased filling pressure) and greater systolic ejection. The fact that the systolic and diastolic diameters tended to change in the same direction during exercise and startle in intact unanesthetized animals (Fig. 3) cannot be rationalized effectively with existing data.

Myocardial Viscosity.—Relaxed myocardial fibers respond to a sudden stretch by a marked increase in tension.[12] Thus, the internal friction within myocardial fibers opposes any sudden change in length, either stretching or shortening (Fig. 5B). At first sight, ventricular distension should be markedly impeded during early diastole when, in fact, the filling is extremely rapid. The sudden transition between rapid filling and slow filling might be due to myocardial viscosity, but this would mean that sudden stretch of myocardium does not occur until filling is largely complete. This possibility will be considered in relation to the effects of interfascicular tension *(vide infra)*. Diminished myocardial viscosity would facilitate diastolic filling and could be another mechanism for neural and hormonal control of stroke volume.

The Law of Laplace.—At the end of systole, the radius described by the myocardial fibers is minimal for that particular cycle. As ventricular filling begins, the effective filling pressure required to overcome myocardial resistance to stretch would be greater than at any other time during the cycle. Actually the filling rate is greatest, and the effective filling pressure is often minimal, during early diastole. It seems clear that little or no resistance to distention is offered by the myocardium during early diastolic filling. The apparent paradox between the early rapid filling, and the theoretical resistance to distention offered by both myocardial viscosity and the relation $P = \frac{T}{R}$ may be at least partially resolved by considering the interfascicular tensions developed during systolic contraction.

Interfascicular Tension.— During ventricular systole, the inner layers of the myocardial bundles are probably under compression and the connections between the various layers under tension. The energy of contraction which is dissipated in the form of interfascicular tension acts to impede systolic ejection, but is stored as potential energy until the ventricles relax. At the beginning of diastole, this potential energy is rapidly released, acting to restore the ventricular chambers toward their diastolic dimensions. Thus, interfascicular tension acts to facilitate rapid filling during early diastole and resistance to distention may be minimal during this phase. If this is true, active stretch on the myocardium due to the effective filling pressure may not begin before the transition between the rapid filling and the slow filling phases. On this basis, more complete systolic emptying would be expected to promote more rapid early filling so that tachycardia would be less likely to encroach on the rapid filling period. This prediction has not yet been confirmed.

Summary

The heart is generally believed to respond to an increased pressure or volume load by distending to greater diastolic volume. This concept is based on experiments conducted on anesthetized thoracotomized dogs in which the heart is characteristically much smaller than under normal conditions. Direct recordings of left ventricular diameter of intact unanesthetized animals demonstrate that during exercise, diastolic diameter did not usually increase. Instead, the systolic diameter appeared to be reduced. Both diastolic and systolic diameters are increased after exercise and after an unexpected loud noise. On the basis of these experiments, it is proposed that stroke volume can be increased by utilization of either the diastolic reserve volume or the systolic reserve volume. Rapid changes in ventricular diameter from cycle to cycle suggest direct effects of neural reflexes on myocardial "distensibility" and "contractility." Some of the factors which influence

ventricular "distensibility" and "contractility" were considered with particular emphasis on possible mechanisms for neural control of stroke volume.

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SYSTEMATIC ERRORS IN FLOW DETERMINATIONS BY THE FICK METHOD

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IN MANY PHASES of cardiovascular investigation, it is essential to make measurements of the rate at which blood flows through an organ. The mounting demand for precision in quantitative physiology causes us to develop new methods of measurement, and to re-examine the accuracy of long-accepted methods. For many years the application of the Fick principle has provided the classical indirect means of measuring blood flow. Other methods have been judged on the basis of their agreement with Fick measurements. Careful workers have recognized the importance of "the steady state" as a prerequisite to reliable determinations. However, either "the steady state" has escaped rigorous definition, or at least the definition has not been widely appreciated.

Until recently, apparently few doubts have been entertained regarding the validity of the conventional application of Fick's law. Lately provocative articles have appeared in the literature which should stimulate a reconsideration of the assumptions underlying the Fick method of determining cardiac output and of the justification for making these assumptions.[2,7]

First, several questions can be asked concerning the usual application of the Fick principle; second, the lines can be indicated which future experimentation might take to throw light on unanswered questions. The discussion may proceed by examining a statement of Fick's law in several forms, and by describing a model to which the law unambiguously applies. The difficulties that obtain in applying the principle to the real physiological system will be demonstrated by considering the discrepancy between the ideal model and its physiological counterpart.

The law of Fick states that the rate of uptake of a reference material by an organ must equal the net rate at which the material is removed from the organ by the blood flowing through it (other paths of removal being excluded). The statement is conveniently expressed as an equation:

$$\frac{dM}{dt} = F_oC_o - F_iC_i,$$

where $\frac{dM}{dt}$ = rate of uptake of reference material by organ in question
F = rate of blood flow
C = concentration of reference material in blood
Subscripts
i and o refer respectively to blood flowing into or out of the organ

This form of the law is applicable to infinitesimal intervals of time, and since means are not available for instantaneous measurement of uptake and blood contents, the equation as it stands is not in a usable form. Uptake and blood contents are measured over an extended period. Thus, in practice, the integrated form of the equation (second equation) is employed.

$$M = \int^{T} (F_oC_o - F_iC_i)\, dt$$

If the rate of flow, F, and the concentrations of the reference material in the blood supplying and draining the organ are independent of time: i.e., constant during the interval of observation, T, these terms may be taken from under the integral sign and the equation reduced to the following simple statement. During the observation the uptake of reference material is equal to the product of: the rate of blood flow, the arteriovenous difference in the concentration of the reference material, and the time interval involved. The equation is then:

$$M = F(C_o - C_i)T$$

In order to arrive at this simplification it was necessary to assume that the flow and concentration were constant. Also, it may be emphasized that the assumption is implicitly made that the measured uptake reflects the net amount of reference material added to the blood flowing through the organ. This is the familiar form of Fick's law which is used for the calculation of flow from these data. In the restricted area of the appli-

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cation of the law of Fick to the determination of flow, it might be asserted that the "steady state" is one in which this usable expression of the principle may be applied without error.

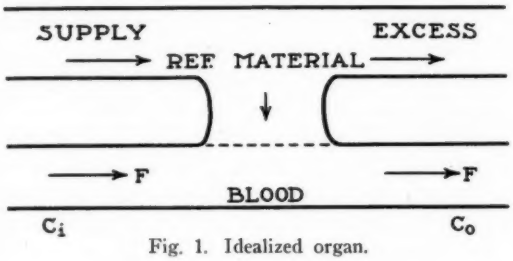

Fig. 1. Idealized organ.

In Figure 1 is shown a simple model which would strictly conform to the restrictions imposed by the assumptions made in deriving the last equation. The essential features are: (1) vessels supplying and draining the organ, (2) a supply of reference material to the organ, (3) a "dead space" or reservoir in the organ of fixed volume both for blood and for the reference material, and (4) constant blood flow and blood concentrations during an observation.

In the actual case, for instance in determining cardiac output by the pulmonary transport of oxygen, it is obvious that these conditions are by no means fulfilled. The cardio-pulmonary system is much more complex than this simple idealized model. In principle, the physiological system is represented in Figure 2, which illustrates some of the pertinent details by which it differs from the simple model.

Under the influence of the cardiac cycle, the respiratory cycle, and from other causes, the lung volume and the pulmonary blood volume change. It is well known from the work of various investigators; for example Greene and Swanson,[3] and Heymans and Jacob,[4] that as a perturbation to the basic respiratory excursions, the mean lung volume undergoes considerable periodic fluctuation with a period equal to several respiratory cycles. Plethysmographic studies indicate the existence of cardiac, respiratory and relatively long term fluctuations in the volume of the extremities. These are consistent with the notion that the pulmonary blood volume undergoes periodic change.

Since in practice the oxygen uptake can only be measured at the mouth or nose, the variable buffer capacity for oxygen of the alveolar space and the pulmonary blood may interfere with the accurate short term measurement of the uptake as referred to the blood flowing to and from the

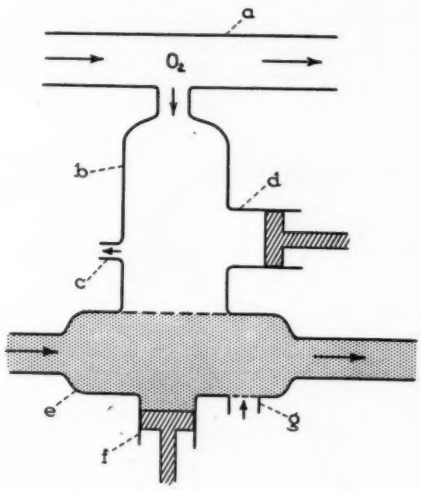

Fig. 2. Schematic representation of cardio-pulmonary system. (a) external airway, (b) total lung capacity, (c) route for direct nonvascular pulmonary, consumption of oxygen, (d) variable part of lung capacity, (e) central blood volume, (f) variable part of central blood volume, (g) drainage of venous blood to left ventricle, through Thebesian veins.

lungs. This question has been raised by Fishman and his colleagues.[2] In order to avoid this type of error it is essential that the amount of oxygen within this buffer reservoir be the same at the beginning and at the end of the period of observation.

Recently, Drs. Visscher and Johnson have initiated consideration and discussion of another important aspect of the total problem.[7] They have pointed out that the usual procedure of sampling blood at constant rate may not yield a sample of the same oxygen content as the average content of all the blood which flows past the sampling site in the collection period. This undesirable situation can occur whenever both the rate of flow and the oxygen content of the blood, passing the sampling site, vary during the sampling procedure.

While this error is *per se* a sampling error, the circumstances of variable flow and concentration, which give rise to it, may also impart an error directly referable to the discrepancy between the ideal model and the real system. For,

the buffer reservoir of the central circulation and lung volume may temporarily absorb, or give up, oxygen, even without an alteration in its volume if the concentration of oxygen in the blood or

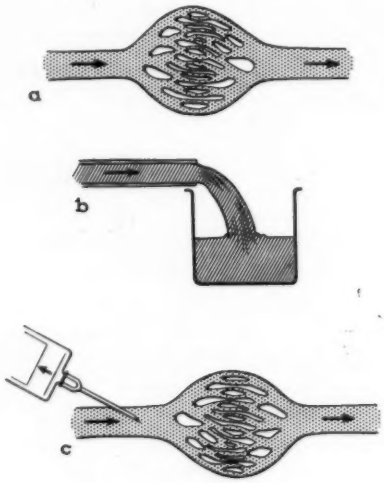

Fig. 3. Hypothetical and actual methods of sampling blood supplying an organ under investigation. (a) the organ with its artery and vein, (b) the hypothetical collection of blood for an arterial sample, (c) the actual collection of an arterial sample in a syringe.

gas in this space undergoes fluctuation. This factor could be expected to contribute a systematic non-random error in the period of changeover from one "steady state" to another, as for instance, in the transient period of adjustment to exercise or to an alteration in the inspired oxygen tension.

To return to the sampling error, its basis can be understood by considering in detail the relation between the collection of the sample and the flow of blood and of oxygen past the sampling site. In Figure 3a, the organ in question is illustrated with the artery and vein which serve it. Focussing attention on the blood in one particular vessel, the flow in the artery may be examined. If, without disturbance, the artery could be severed and the blood flowing through it caught in a beaker for the same length of time that the sampling procedure would ordinarily require, after this interval the beaker would contain the same volume of blood and the same amount of oxygen as otherwise would have entered the organ. This hypothetical procedure is shown in Figure 3b. This would be true regardless of variations in flow or oxygen content during the collection. The average content of the blood in the beaker, multiplied by the volume of blood, would equal the quantity of oxygen which would have entered the organ in the collection interval. It is precisely this concentration that is required in the calculation of blood flow from the simplified equation expressing Fick's law for extended periods of time.

In actual practice a needle or a catheter is inserted in the artery and blood is withdrawn at approximately constant rate (Fig. 3c). In the presence of variable flow and oxygen content, the average content of the sample thus obtained might not be the same as that of the blood in the beaker. The discrepancy between the two occurs due to the fact that the flow into the syringe, , *is not* always proportional to the flow in the vessel, F. The syringe sample would yield the *time average concentration*, whereas the sample from the beaker would have the *volume average concentration*. The time average concentration is equal to the quantity of oxygen in the syringe divided by the volume of blood in the syringe. The equivalent equation is:

$$\overline{C^t} = \frac{\int_0^T \mathcal{F} C\,dt}{\int_0^T \mathcal{F}\,dt} = \frac{\int_0^T C\,dt}{T}$$

where

$\overline{C^t}$ = the time average oxygen content
$\mathcal{F}$ = constant rate at which the syringe is filled
C = instantaneous oxygen content
t = interval of observation.

The volume average concentration is equal to the quantity of oxygen in the beaker divided by the volume of blood in the beaker. Or expressed as an equation:

$$\overline{C^v} = \frac{\int_0^T FC\,dt}{\int_0^T F\,dt}$$

where

$\overline{C^v}$ = volume average concentration
F = instantaneous rate of flow from the artery.

An exact expression can be obtained for the difference between these two average concentrations. Let the flow, at any instant, be represented as the sum of the average flow over the entire interval of observation, plus the instantaneous deviation from the average. Likewise, let the oxygen concentration at any instant be similarly rep-

resented as the sum of the average (this will be the time average), and the instantaneous deviation from the average. Thus:

$$F = \overline{F} + \delta F$$

$$C = \overline{C^t} + \delta C$$

By substituting these expressions for flow and concentration in the formulas for the time and shows by means of a graph the assumed patterns of flow and concentration. The abscissa is proportional to time, the ordinate scale at the left gives the instantaneous flow corresponding to the upper line, while the ordinate scale at the right represents the instantaneous value of the concentration. The amplitudes are designated A and B and the phase angle by which the concentration

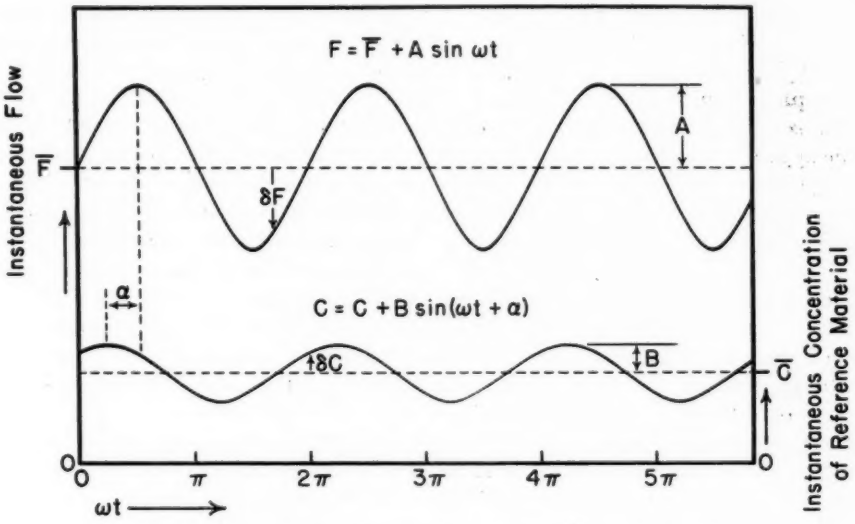

Fig. 4. Assumed sinusoidal variations in flow and concentration.

volume average concentrations, the difference between these two quantities, ΔC is obtained.

$$\Delta C = \overline{C^t} - \overline{C^v} = -\frac{1}{\overline{F}T}\int^{T} \delta C \cdot \delta F dt.$$

This formula is quite general and it is applicable to any specific situation involving a discrepancy between time and volume average concentrations. Unfortunately, from a practical point of view, this result indicates that detailed knowledge regarding the flow and the concentration of the reference material is needed in order to estimate the magnitude of the error incurred by using time average rather than volume average concentrations.

In order to illustrate the meaning of this expression, a calculation has been made for a hypothetical case of sinusoidal variations of the same frequency in concentration and flow. Figure 4 wave leads the flow wave is given as α. For this case:

$$\Delta C = -\frac{AB\cos\alpha}{2\overline{F}}.$$

Since the discrepancy between the time and volume average concentrations is proportional to the cosine of α, it is evident that the time average concentration may be larger, smaller or the same as the volume average concentration depending on the value of α.

A general expression can be obtained for the fractional error in the calculated flow or output by considering the error due to the use of time average concentrations for both arterial and venous blood. The correct formula for average flow is:

$$\overline{F} = \frac{M}{T(\overline{C_o}^v - \overline{C_i}^v)}.$$

The incorrect formula utilizing time average concentrations is:

$$\overline{F^*} = \frac{M}{T(\overline{C_o}^t - \overline{C_i}^t)}.$$

The fractional error in flow is obtained by combining these expressions with $\triangle C$ as defined above.

$$\frac{\overline{F^*} - \overline{F}}{\overline{F}} = \frac{\int_T (\delta F_o \cdot \delta C_o - \delta F_i \cdot \delta C_i)\, dt}{M + \int_T (\delta F_o \cdot \delta C_o - \delta F_i \cdot \delta C_i)\, dt}$$

Only the sampling error has been considered in arriving at this result. The last formula cannot of course be applied in practice. However, it may serve as a guidepost in estimating the limiting error of this type when some of the details of flow and concentration at the sampling sites are known.

Within the framework of these formal conclusions, it is of interest to examine some of the factors which may produce fluctuations in flow and concentration and some of those which tend to smooth out or otherwise annul the effects of the variations. Although insufficient data are available to assess the importance of the various factors, it is perhaps justified to speculate briefly concerning them.

Arborization is one of the cardinal features of the vascular system. Both a branching in the arterial tree, and a confluence in the venous system, are possible sources of difficulty as related to the subject of the sampling error. First, consider a confluence in the venous system. If the oxygen contents of the blood flowing in the tributary vessels are different, any variations in the relative contributions of the small veins to the flow in the main vessel will produce fluctuations in the oxygen content of blood flowing in the larger vessel. Thus it is possible that such a site is the origin of concentration differences in the venous circulation. This situation is apt to occur in the case of the vena cavae and coronary veins supplying blood to the right atrium.

At a bifurcation in the arterial tree, the same process in reverse may be operative. If concentration waves are present in the parent artery, any time variation in the relative flow into the daughter vessels would result in differences in the average saturations of the blood flowing in the two smaller arteries. In this way, it is seen that a sample withdrawn from a peripheral artery might not be equivalent to one obtained from the main arterial stream.

In addition to this effect, systemic arterial blood may be subjected to variations in oxygen content in the process of becoming arterialized in the pulmonary capillaries. Information is lacking regarding fluctuations of the frequency of the heart rate, but in earpiece oximetry, undulations in oxygen saturation of respiratory frequency are sometimes observed even in normal subjects at rest breathing air. This finding is substantiated in the theory of respiratory gas exchange which indicates that substantial variations of this frequency may occur in arterial gas contents.[1,6]

Turning now to the question of the inconstancy of flow, recently, careful dynamic flow measurements made in animals have been reported. For example, McDonald[5] presents data obtained by high speed cinematography of the flow pattern in the abdominal aorta of the rabbit. He made simultaneous measurements of the velocity and pressure just distal to the origin of the renal arteries. His data clearly show that at the site of observation the pressure and velocity waves differ both in phase and form. Thus, in general the sampling error could not be avoided by merely allowing the variable pressure head to deliver the sample. Elimination of the error would require collection at a rate always proportional to the flow at the sampling site.

Thus far only those factors have been considered which emphasize the sampling error. There are, however, several ways in which the causes for error are dissipated. As the blood moves away from the source of time variations in composition, it travels with different velocities in the various lamina. The more peripherally the blood moves, the less pronounced the inequalities in composition become due to longitudinal mixing. Also, for instance, in the case of systemic arterial fluctuations in oxygen content, the differences in the path length from various pulmonary capillaries to the sampling site, tend to randomize the initial inhomogeniety.

A final point is worthy of mention. Previously attention was drawn to the importance of the separation in phase between undulations in flow and concentration in determining the magnitude and direction of the sampling error. This difference in phase is principally determined by two factors: (1) the velocity with which the flow

and concentration waves travel (the concentration wave moves with the mean blood velocity while the flow wave moves considerably faster at approximately pulse wave velocity); (2) if the basic causes for the existence of these waves were of constant frequency, then the phase angle between the two would be constant at any particular site. However, the periods of physiological oscillations including the heart beat and the respiratory excursion are never precisely constant. Thus the phase angle even at one site would vary. This factor would also aid in randomizing the sampling error and hence in reducing its over-all effect.

Unfortunately, the status of this subject at present is decidedly uncertain. Whether there is appreciable error in the usual applications of the Fick principle is a matter of conjecture. Obviously, there are possible causes for error. An answer to the questions that can be raised may come from either of two directions. It would be helpful to compare the results of Fick measurements with a reliable direct method of determining blood flow at various levels of activity and with different inspired gas mixtures. Direct assessment of the significance of the sampling error can only be made on the basis of simultaneous dynamic measurements of flow and oxygen content at various places in the vascular system.

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CONGENITAL CARDIAC DEFECTS—REFERRALS AND RECOMMENDATIONS

The general practitioner will not see many cases of congenital heart defect in his practice. When he does see one he is confronted with these questions: Is the murmur indicative of a serious defect? Is this an operable condition? Should the patient be referred for consultation? What shall the parents be told? How much activity should the child be permitted?

Any cyanotic type of heart lesion is serious, but only certain types may be operated on at present with the expectation of good clinical results.

In general, intense cyanosis, or an enlarged heart or an abnormally shaped heart on fluoroscopic examination is indicative of a serious congenital heart defect. These cases should be referred for consultation to a cardiologist familiar with hear disease in childhood, and the decision as to the necessity for special diagnostic procedures should be left to him. Parents should be told of the presence of a congenital cardiac defect, informed that it is not a disease, and a definite effort should be made to explain to them the nature of the defect, serious or otherwise. If informed by the family doctor whom they know and trust, the parents will be far less upset than if they learn of the defect through a routine school or club examination. The general practitioner is advised not to bring up the necessity for surgery before consultation unless he is sure of the exact diagnosis.

If the family physician plans to refer the child to a specialist, he has to be on his guard when he discusses his diagnosis with the parents or mentions the possibility of surgery to them. Because he wishes to persuade the parents to consult a specialist at once, he may be tempted to make a strong statement, but he will do much harm to the patient and the family if he tells them bluntly that the child has a heart condition and must have an operation or he will die. Cases of congenital heart defects are rare in his practice and the family physician often has no means of verifying the diagnostic impression gained from the history and the physical findings. There is always the chance that the diagnosis may be wrong and, even if it is correct, operation may not be indicated or may not be feasible.

Younger children with congenital heart defects rarely need to be limited in their daily activities by the physician or parents, as they will automatically limit themselves; this is especially true of children with cyanotic lesions. They need not be told to sit down and rest; the development of dyspnea will make them rest of their own accord. Older children with congenital heart defects, resulting in an enlargement of the heart, should not be permitted to take part in competitive sports, since their pride may force them to continue beyond their physical capacities.

Children with minor cardiac defects, such as a small ventricular septal defect, may be as active as they wish. Far greater harm will be done to the child if he is continually admonished to "be careful—go slowly" than if he is left on his own. These children do not need monthly physical check-ups except under special circumstances. School health slips should be carefully filled out, and emphasis laid on the degree of activity permitted; otherwise the teachers will tend to refuse to permit the child to join in any play.

If tooth extractions or operations such as tonsillectomy are indicated, they need not be avoided. Anesthetics may be administered safely to these children. Prophylactic medication should be given before and after the surgical procedure to avoid subacute bacterial endocarditis to which these children are especially susceptible.

The child with a congenital cardiac defect has been handicapped by nature. Every effort should be made to avoid creating an additional handicap by unnecessary restrictions. He should be allowed to live as active a life as possible.—From "Diagnosis of Congenital Cardiac Defects in General Practice," American Heart Association.

THE PHYSIOLOGY OF CONGESTIVE FAILURE OF THE CIRCULATION

W. F. HAMILTON, Ph.D.

Augusta, Georgia

I AM GREATLY HONORED to be asked to come to the University of Minnesota to deliver a talk on the Physiology of the Circulation. It is like carrying coals to Newcastle because work in this field has been very important in both the Rochester and the Minneapolis branches of the University.

I am particularly pleased that this lecture is dedicated to Dr. Fahr. For many years it has been my pleasure to look for him in the Federation meetings, to greet him as a friend, and then proceed to reap the riches of this great mind. I salute him as a great teacher, one who delights to share his very sound ideas and is ever patient and helpful to his younger associates.

My topic, the Physiology of Congestive Failure of the Circulation, is one about which there is much debate at the present time. Particularly is this true about edema. Our textbooks would have it that a high venous pressure will *ipso facto* result in edema by raising capillary pressure and augmenting filtration of fluid from the vascular system into tissue spaces. This oversimplified idea is attributed to Starling—though, in his original description of "Physiological Factors in the Causation of Dropsy,"[28] he stresses the unbalance between ingested water in excess of that excreted by the kidney. This produces hydremic plethora, which increases venous and capillary pressure. The resulting excessive transudation, according to Starling, leads to dropsy.

Since edema is constituted of large quantities of interstitial saline solution, we must agree with Starling that its accumulation of necessity results from intake of water and salt being greater than output. In heart disease it would seem that this unbalance is due to lessened renal output rather than to increased intake.[23]

Three ideas are ascendent as to the cause of renal retention of salt and water: (1) pre-renal deviation, (2) alteration of renal hemodynamics, and (3) hormonal disturbances. It may be that the adrenal gland or the pituitary gland secretes the key hormone.

In thinking of pre-renal deviation of salt and water, one meets the suggestion that the fluids are sequestered in the interstitial spaces so that they cannot get to the kidney. The cause is said to be high venous and capillary pressure resulting in transudation which not only causes the accumulation of dropsical fluids but also prevents their return to the bloodstream and kidney.

However, one does not need a high venous pressure in order to sequester fluids in the interstitial spaces. When one drinks a glass of water, or submits to an infusion, the fluid passes at once out into the interstitial spaces, and expands either the total body water (H_2O, D_2O) or the extracellular fluid (saline). It does this at a very rapid rate and with no measurable increase in venous pressure. Extra salt water is all that is needed to increase the extracellular fluid volume, and the reduction of this fluid volume is the simple result of getting rid of the salt water. This happens in heart disease by bed rest, digitalis, or diuretics in spite of a venous pressure persisting above normal levels. It happens in nephrosis spontaneously with the venous pressure normal during the accumulation and disposal of the dropsy.

The effect of increasing renal venous pressure upon sodium resorption is a temporary sodium retention when a ligature is placed around the cava just above the renals,[18] but this is permanent if the constriction is made above the liver,[5,27] indicating that renal venous pressure *per se* is not the key stimulus to edema formation. Temporary oliguria with sodium retention also results from exercise,[30] venous congestion of the extremities,[29] and pressure on the abdomen.[2] This last has been looked upon as illustrating the effect of increased venous pressure[2,26] but, since the kidney and vena cava are subject to the same ambient pressure, it is hard to see how the effective renal venous pressure can be increased by this maneuver. The ef-

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The experimental work outlined in this paper is a co-operative venture of the Departments of Physiology and Thoracic Surgery of this school. Participating were R. G. Ellison, R. W. Pickering, E. E. Hague, and J. T. Rucker, Jr. It was made possible through grants from the U.S.P.H.S., and from the Life Insurance Medical Research Fund.

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Dr. Hamilton is Professor of Physiology at the Medical College of Georgia.

fective arterial pressure, however, is lowered by the amount of the externally applied pressure as the arteries enter the abdomen.

Alternatively, retention of salt and water is said to be the necessary result of changes in renal hemodynamics. Thus, it is more difficult to get rid of sodium when there is lowered renal blood flow. Lowered blood flow lowers the filtration rate, ultimately, though the filtration fraction is increased. When the lowered filtrate formation displays sodium before the tubules in less amount than is their obligate reabsorptive function, a minimal amount of sodium is cleared from the body.[20]

As a general rule the glomerular filtration rate is reduced in congestive failure. However, in patients regaining compensation, sodium may be released with no consistent change in filtration rate. This is true whether the sodium load is high[3] or low[25]—whether filtration rate is measured by sodium thiosulfate,[3] inulin, or creatinine.[26] Tubular resorption of sodium (and water), through it is often more complete with low filtration, may be entirely independent of filtration.[3,7,12,13,25] This indicates that the resorptive mechanism is under direct physiological control and is not an obligate function of filtration rate. The fact that sodium excretion may be independent of filtration rate is further evidenced not only by the fact that subjects with low filtration rate will release sodium as they recompensate under the influence of bed rest, as well as after digitalization, and after the immediate influence of mercurial diuretics have passed off,[3] but also by the fact that circulatory handicap will lead to sodium retention even though filtration is normal.[5,13]

The evidence that the retention of salt and water is due to either prerenal deviation or to exclusively hemodynamic factors is not conclusive. Tubular function and the renal circulation seem, moreover, to be remote in their control from neurogenic factors—at least in the steady state.[30]

This leaves hormonal factors. The pituitary gland may play a key role. The posterior pituitary gland seems to be controlled by osmoreceptors[30] in its liberation of antidiuretic hormone promoting tubular resorption of water. Sight should not be lost of a possible mechanism involving the liberation of adrenocorticotrophic hormone to control the resorption of salt.

Conclusive evidence that the posterior lobe plays a role in the edema of circulatory failure is lacking. Presumptive evidence of its own activity is that the plasma sodium is often low in congestive failure and yet the patient suffers from chronic oliguria with antidiuretic substance in the plasma.[19] This would imply that some factor in heart disease stimulates the hypothalamo-pituitary mechanism to conserve water in greater amount than that needed to preserve the isotonic state.

That the adrenal does play a rôle is suggested by the fact that, when desoxycorticosterone acetate is given in excessive amounts to Addisonians, there result all of the signs of congestive failure of the circulation.[4] Remission of these signs occurs as soon as the drug is withdrawn.

It has also been shown by Davis and Howell,[5] that chronic passive congestion of the abdominal viscera, produced by partial obstruction of the thoracic inferior vena cava, caused retention of sodium and water. Upon adrenalectomy,[6] and the administration of cortisone, there was a prompt loss of sodium and water. Addition of desoxycorticosterone acetate in larger amounts than for ordinary maintenance, caused retention at a rate similar to that shown before adrenalectomy.

From the foregoing it would seem that a circulatory handicap may result in retention of salt and water with the formation of edema, and that the function of the adrenal gland, and possibly the pituitary, are important factors in this response.

In the hope of gaining insight into the physiology of the ascites of mitral stenosis, experiments outlined below were made on dogs. It was found, in brief, that when the mitral valve was gradually narrowed to a size comparable with that seen in severe clinical mitral stenosis, the animal became oliguric, excreted small amounts of sodium, and developed ascites. This occurred with normal venous pressures and could be reversed by withholding sodium or removing the adrenals, or simply by loosening the ligature. We have been unsuccessful so far in getting an animal to become ascitic, even with extreme stenosis, while afflicted with diabetes insipidus.[11,15,16,21,22]

The surgical operations described below were carried out by Dr. R. G. Ellison, whose work was a keystone in the investigation. Indispensable also were the constructive ideas and careful, painstaking work of R. W. Pickering, E. E. Hague, and J. T. Rucker, who took major responsibilty

in the cardiorenal studies detailed herein.

For a long time it has been known that the mitral valve can be constricted sufficiently to give evidence of stenosis (early literature[9]), but without any clinical deterioration of the animal. It was found by Haddy and colleagues[14] that in animals in this condition, even though the mitral valve was constricted enough to increase the pulmonary venous pressure, the cardiac output and clinical condition remained normal. It has been our experience,[9] confirmed by Haddy et al,[14] that if an acute constriction of the mitral valve was produced, so that its aperture was of the order of 1 cm^2/m^2, the animal died promptly of pulmonary edema.

We were interested in the occurrence of congestive failure after mitral stenosis. It seemed possible that the signs of this condition might appear if (1) the valve was not constricted at the time the animal was faced with the added handicap of deep anesthesia and post surgical shock, and (2) if the valve were constricted gradually and in such a manner that the constriction could be loosened when the signs of pulmonary edema appeared.

Operations

In order to do this, an operation was devised which is described elsewhere[9,10,11,15,16,21,22] and may be briefly outlined here. A special ligature was prepared, consisting of 28G stainless steel wire encased in 18G nylon tubing. Two 18G sharp needle tubes were pushed snug against the nylon tube and crimped in place on the wire.

The dogs were anesthetized under 10 mg/Kg. morphine and 20 mg/Kg. pentobarbital. The chest was opened aseptically by a rib spreading incision in the fifth interspace. The pericardium was opened and the ligature was threaded through the right auricle as near the septum and the floor as possible. (Fig. 1). It was drawn around the mitral ring and held in place by passing it under the epicardium in two or three places. The ends of the ligature were then drawn through a telescoping adjustable silver tube, one end of which was placed against the heart to hold this organ in place, and the other end between the fifth and sixth ribs and under the skin. The ligature was drawn snugly about the valve ring. The needles were cut away and a silver clip was bent around the ligature ends to hold them in place. The incisions were all closed with the usual surgical precautions.

When all wounds had healed and the animal seemed in good shape, the skin over the end of the tube was anesthetized, or light general anesthesia given, and the ligature ends exposed. They were then drawn tight enough so that a persistent (two or three minutes) weakening of the femoral pulse occurred. The ligature ends were re-clipped in the new location. This tightening was repeated at weekly intervals. The narrowing was 2 or 3 mm. above the mitral ring and left the leaflets functional. The mitral orifice was reduced in size comparably to that seen in severe clinical mitral stenosis (Fig. 2) and showed a murmur typical of the clinical disease (Fig. 3). The table indicates the pertinent facts relating size of the stenosis with the condition of the animal. The conclusion seems fair that when the mitral aperture is narrowed gradually it may be reduced to a very small size without producing acute pulmonary edema, whereas, as seen above, when it is constricted at the time of the operation, pulmonary edema and prompt exitus result even though the mitral orifice is

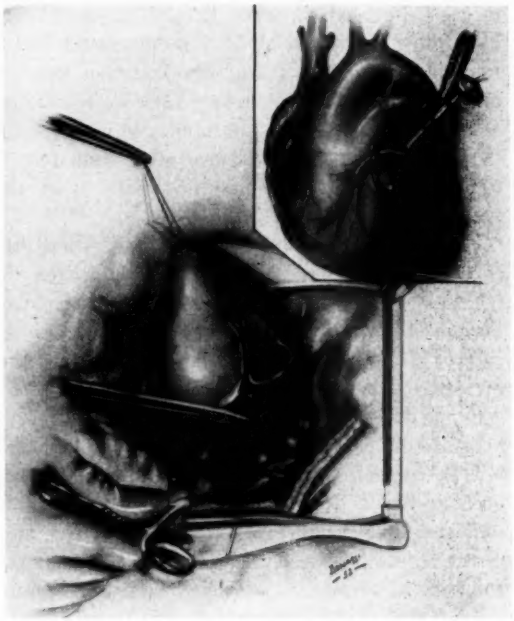

Fig. 1. Exposure of heart and placement of stenosing ligature (See text). Reprinted from Surgical Form.[10]

relatively large. The animals whose valves were gradually constricted developed a chronic state resembling, in some aspects, congestive failure of the circulation. After each tightening, there

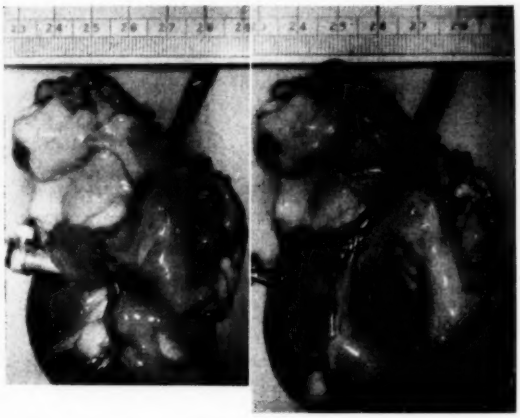

Fig. 2. The mitral orifice in mitral stenosis of controlled degree (right) as compared with a normal orifice. Reprinted from Surgical Form[10].

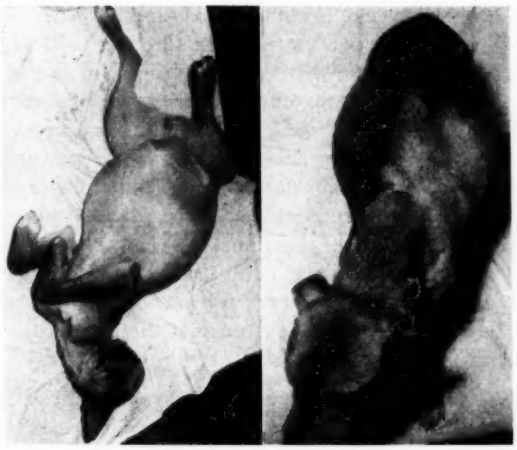

Fig. 4. Ascitic dogs with experimental mitral stenosis.

was an evanescent sodium retention and occasionally the temporary presence of ascites could be demonstrated. After a variable number of tightenings, urinary sodium excretion diminished to very low levels, and ascites accumulated prodigiously at a rate of sometimes 1.4 liters per week (Fig. 4). The ascites could be relieved by regular paracentesis or its formation prevented by administration of ion exchange resins and the animals kept alive from three to thirteen months.

Except for those that were sacrificed, nearly all of the dogs died of terminal pulmonary edema. In two cases, a clot was found at autopsy causing an obstruction of mitral orifice further than

Fig. 3. Murmur typical of mitral stenosis from experimental dog, with simultaneous electrocardiogram.

that indicated by its anatomical measurement. The others may have had such a clot which was lost at autopsy. Another fact may explain the pulmonary edema. During the chronic course of the experiment, the plasma proteins gradually fell to low levels. This, by reducing the coloidal osmotic pressure, may have rendered the animals vulnerable to pulmonary edema at pulmonary vascular pressures not ordinarily dangerous.

Attention should also be called to the dog (H-9) whose pituitary stalk had been cut with probable injury to the hypothalamus. This animal had severe diabetes insipidus. It received a protracted series of seven tightenings, reducing the mitral orifice to a figure well below that associated with ascites in most of the other dogs. It may be that ascites is incompatible with diabetes insipidus.

The most obvious suggestion as to the cause of the ascites is that it results from simple filtration caused by a high venous (capillary) pressure. The venous pressure at the portals of the heart and the end-diastolic (filling) pressure in the right ventricle were not, however, above normal limits (Table I).

Not only was the central venous pressure normal, but there were none of the classical signs of chronic passive congestion. The spleen, kidney and liver were of normal appearance and size, grossly. The only microscopic abnormality was an obscure spotty hyperemia of the hepatic sinusoids and a complex convolution of the paralob-

TABLE I. CIRCULATORY AND RENAL EFFECTS OF EXPERIMENTAL MITRAL STENOSIS

Dog		No post-op. tight-enings	Area mitral orifice mm^2/m^3	Cardiac index	Ascites duration days	Pressure mm Hg			Clearance cc/mm				Plasma Protein G%		Urinary Sodium mEg/day	
									Creatin		PAH					
No.	Wt. K					RA diast.	RV-PA syst.	PA diast.	Control	Failure	Control	Failure	Control	Failure	Control	Failure
59	—	4	65	—	150	0	38	15	—	—	—	—	—	—	—	—
74	14	1	21	—	90	0	28	10	—	—	—	—	—	—	—	—
75	15	2	21	—	60	3	40	16	—	—	—	—	—	—	—	—
76	14	2	47	2.2	20	2	34	12	—	—	—	—	—	—	—	—
82	13	3	35(clot)	2.6	30	0	30	—	31	22	119	73	—	4.1	51.0	1.7
83	15	3	55†	2.0	60	1	24	7	41	32	130	141	—	4.6	57.0	1.9
86	12	2	90	—	48	‡	—	—	48	10	120	50	—	3.4	34.0	1.5
94	8	1	—	3.2	365†	0	32	16	17	16	101	65	5.4	4.2	161.0	3.0
99	10	2	94	2.4	37	3	31	15	21	29	137	107	6.9	3.6	66.0	2.3
108	13	3	47(clot)	—	6	‡	—	—	29	35	164	154	5.7	5.4	42.0	1.1
110	13	1	86	2.0	30	0	26	8	27	18	137	97	6.1	4.0	4.2	0.7
111	15	4	99†	—	14#	‡	—	—	23	29	88	91	5.7	4.5	79.0	0.7
112	14	3	300*	—	12#	‡	—	—	35	33	157	147	6.2	4.8	41.4	0.4‡
H9	15	7	19	—	0	‡	—	—	33	—	128	—	6.2	—	61.3	—

†Tricuspid stenosis also. *Suture broken. ‡Jugular pressure normal. #Adrenalectomy.

Dog No.	Remarks
59	Terminal pulmonary edema
74	Terminal pulmonary edema
75	Interstetial edema cachexia TPE
76	Gangrene (sacrificed)
82	PE (due to mitral clot)
83	Gut hemorrhage after paracentesis
86	Cachexia TPE
94	Alive and well. Ascites controlled by carboresin
99	Sacrificed
108	TPE (mitral clot)
110	Sacrificed
111	Sacrificed Adrenalectomy
112	Sacrificed Adrenalectomy
H9	Experimental diabetes insipidus—no ascites

ular venous channels. This affected only a few among many quite normal lobules. When ascites is produced by clamping the thoracic inferior vena cava and raising the abdominal venous pressure, the abdominal organs show clear signs of chronic passive congestion.[31]

On the other hand, when the dog was in the supine position the femoral venous pressure was definitely elevated. Nevertheless, edema of the feet and legs was not conspicuous.

The elevated femoral venous pressure is hard to explain except as the result of an increased pressure in the abdominal vena cava. The likelihood of this is enhanced by the fact that the superficial network of veins in the abdominal wall were greatly dilated, serving no doubt as a collateral drainage of the hind quarters.

To measure the pressure in the abdominal vena cava, a Cournand catheter was passed via the jugular vein, beyond the diaphragm, and the pressure was recorded. The abdominal caval pressure responded to manual pressure against the abdomen and, with the animal in supine position, varied from 12 to 14 cm. H_2O above the level of the catheter tip in the vena cava.

Now when the catheter was drawn into the thoracic part of the vena cava, the pressure fell to the normal venous pressure value (the height of the apex beat) or 6 cm. above the vena cava. There was a fall in pressure between that in the abdominal and thoracic inferior vena cava. It was caused, no doubt, by the fact that the contents of the distended abdominal cavity transmitted a pressure nearly equal to that in the vena cava, collapsing its walls about the contained blood, and contributing largely to the pressure measured in the great vein. As the blood approached the diaphragm the down stream pressure was reduced, the velocity increased, and the loss of lateral pressure (Bernoulli effect) caused further collapse of the vein around a fast jet of blood entering the inferior thoracic vena cava which was not subject to high outside pressure. Back pressure from this jet is responsible for the fact that pressure throughout the abdominal vena cava is slightly above that in the abdomen.[8,17] In the thoracic vena cava, blood pressure is not subject to conspicuous changes from abdominal manipulation as is the case in the abdominal vena cava.

The same experiment was performed on another dog whose belly was very tense. The pressure in the abdomen was 13 to 16 cm. H_2O of which 10 cm. could be accounted for by hydrostatic factors. The abdominal vena cava and abdominal pressures responded similarly to abdominal manipulation. The vena cava pressure (13 to 17 cm.) was not greatly different from that in the abdominal cavity, allowing for the hydrostatic weight of the abdominal contents. The difference between the thoracic and abdominal caval pressures was greater than in the first animal persisting in the natural position. Thoracic inferior vena cava pressure responded less than abdominal to pressure against the abdominal wall.

In whatever position, the caval pressure became nearly equal to that in the auricle as soon as the catheter tip passed the diaphragm, indicating that the ligature in no way interfered with the return

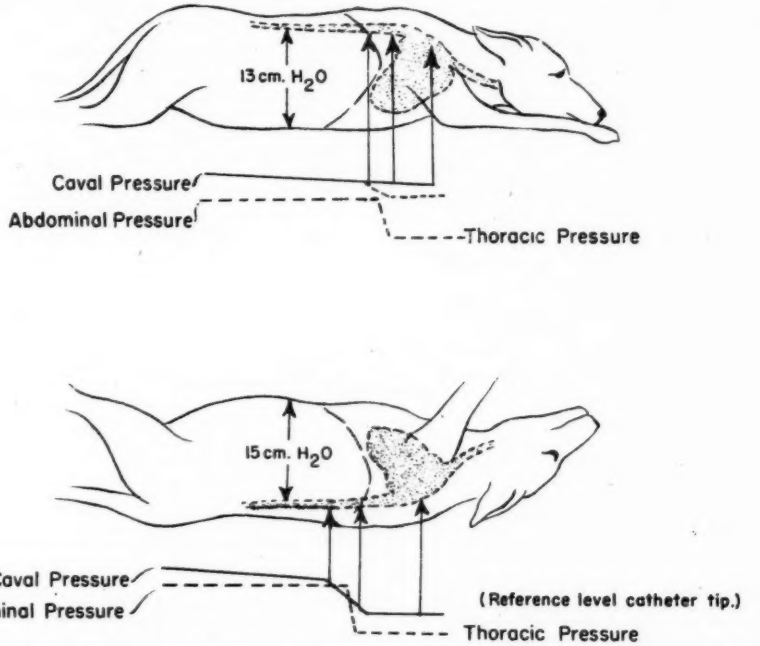

Fig. 5. Diagramatic representation of the fact that, though the pressure in the vena cava is high in ascitic dogs, it does not exceed by more than a few cm. H_2O the pressure in the abdominal cavity and, hence, cannot be responsible for the formation of ascites by simple filtration. Above animal in natural position; below, in prone position.

of blood along the inferior vena cava, and that the high inferior vena cava and femoral pressures were due to the outside pressure from the abdominal contents.

The table illustrates other hemodynamic findings. Although the cardiac filling pressure is low, the pulmonary vascular pressures are somewhat elevated. The cardiac output is at, or slightly below, the low normal level (pentobarbital anesthesia). It is hard to see anything in the hemodynamic picture to cause the ascites. The fact that the arteriovenous oxygen difference is wide, and the mixed venous O_2 tension low, may play a rôle.[8]

Without venturing an hypothesis as to how the direct effects of the ligature produce it, we have evidence that there are changes in renal function which occur with the development of ascites.

The renal blood flow and filtration rates were measured by the clearance of paraaminohippuric acid and of endogenous creatinine. The dogs were trained to lie quietly on the table while samples were being taken. As will be seen from the table, both of these measurements tended to be low in dogs with ascites, but rarely did they fall below the lowest measurements seen in normal control. The kidney seems to have handled blood and filtrate in an essentially normal manner. The reabsorption of sodium (and water) seem to be the renal functions which are most greatly changed. The renal tubule, in response to an unknown mechanism, has been stimulated to reabsorb sodium (and water) from the glomerular filtrate almost completely. Water and sodium seem to have been handled by the kidney in a coordinated manner because, whether the animal was gaining his ascitic pool or losing it, the plasma sodium remained within normal limits. Only the adrenalectomized animal had a low plasma sodium.

The chronically ascitic animal can be made to lose his pool of ascitic fluid. Attempts to cause this by the administration of digitalis or of mercurical diuretics were of no avail. The diversion of dietary sodium into the feces by means of ion exchange resins (carbo-resin, Lilly) often resulted

in a dramatic drying out of the animal. The protocol in Figure 6 illustrates some of the things that happened in our experience.

When the ligature was first tightened, the animal retained sodium for a day or so and then excreted it in excess. A second tightening resulted in the same response, followed by erratic urinary levels which finally eventuated in almost complete sodium retention and the formation of ascites. The body weight increased, the plasma protein level decreased, and the abdomen swelled conspicuously. As carbo-resin was administered, the sodium output (fecal) came into balance with the intake, the body weight leveled off, and the plasma protein returned to normal levels. Another dog whose response to carbo-resin was better (broken line), lost weight on the exhibition of the ion exchange resin, her ascitic pool was evacuated and her plasma proteins, after an overshoot, returned to normal values, which persisted as long as the resin was administered. Withdrawal of the resin caused this animal to become ascitic with low plasma protein levels. Animals can be induced to go through this cycle several times.

A similar cycle occurred when two dogs frayed their ligatures in two, releasing the mitral stricture. The sodium balance was restored by urinary excretion of sodium rather than fecal loss. The clinical picture was similar in that both animals lost their ascitic fluid and had an episode of concentrated plasma protein, which soon returned to normal. The animals became in all respects normal except for the hardware in their chests.

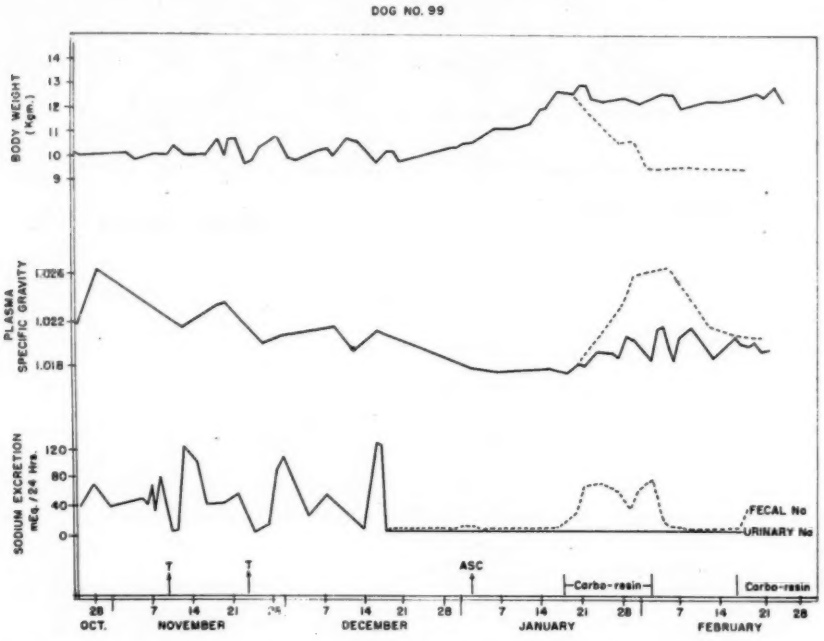

Fig. 6. The course of body weight, plasma specific gravity and sodium excretion in response to the administration of carbo-resin (Lilly). The dog indicated by the solid line was followed through the whole experiment. The dog indicated by the dotted line responded better to the resin (See text).

A very curious event occurred in the case of three dogs. In two animals, after two or three tightenings, no effect on the femoral pulse resulted from further tightening. On a later attempt the ligature came out in our hand. We were amazed to find it unbroken. It had evidently sawed its way through the auricle, much as a weighted string pulls through a piece of ice. The heart healed behind the ligature as it worked through the auricular walls and septum. The animal became quite normal and showed no signs of discomfort. In the case of the third animal the unbroken ligature was found free of the heart at autopsy.

The ascites began to form when plasma protein and venous pressure were within normal limits. Moreover, when carbo-resin was displayed, or when the ligature broke, the animals had an ascitic

fluid whose protein concentration (normal AG ratio) was only 1 to 1.5 per cent lower than that in the plasma. The relation between hydrostatic and osmotic pressure was such as might be expected to lead to filtration. Nevertheless, the ascitic fluid was promptly evacuated as soon as the effective sodium intake was lowered or, in the broken string animals, as soon as the hemodynamic picture was made more nearly normal. This would seem to be brought about by a lessening of the stimulus (whatever it is) which causes the tubule to resorb water and sodium.

The immediate cause of the change in tubular resorption is probably hormonal. The amorphous part of the adrenal secretion is usually regarded as controlling the resorption of salt, and the posterior lobe hypothalamic mechanism probably controls the resorption of water. Neither salt nor water can be resorbed alone, but excess of adrenal hormone may cause the resorption of sodium followed by water, and excess of the pituitary hormone may cause resorption of water followed by salt. The pituitary mechanism has been implicated when plasma sodium levels, in congestive failure patients, are low and the plasma antidiuretic titer high.[19] The adrenal mechanism has been implicated by experiments that show that disoxycorticosterone acetate will produce edema, pulmonary congestion, and enlarged heart, making up the syndrome of congestive failure.[4]

Our dogs with mitral stenosis had normal sodium levels in their plasma. It was therefore decided to test both the pituitary mechanism and the adrenal mechanism.

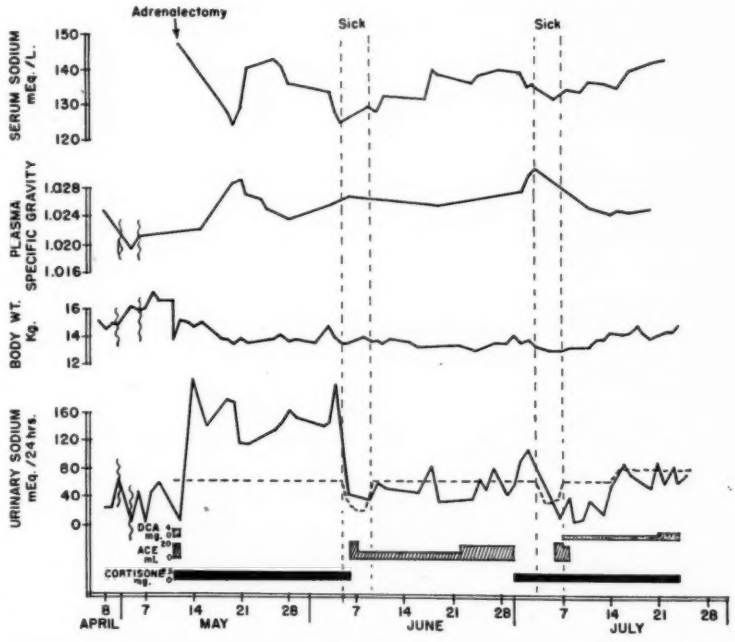

Fig. 7. Effect of adrenalectomy and substitution therapy in dogs with ascites from experimental mitral stenosis. (For details, see text.)

After several attempts to get diabetes insipidus with hypothalamic injury and stalk section, by means of an operative approach with direct vision and by means of a stereotaxic instrument, two dogs, one of which died before the experiment was complete, were prepared with clinical evidence of the disease. On the surviving dog, the ligature, previously placed around the mitral valve, was tightened seven times at intervals of a week or more. She finally succumbed to pulmonary edema. At autopsy the mitral aperture was only 8 sq. mm. (19 mm^2/m^2), a size much smaller than those found in most of our other ascitic dogs. During nine weeks the tightening was repeated to produce sustained weakening of the femoral pulse, and no retention of sodium or formation of ascites occurred. Less than four such tightenings always produced ascites in our normal animals. We are

left with the hypothesis that diabetes insipidus protects against sodium retention and ascites formation. During the last three days of the animal's life, urinary sodium was low but the belly was dry post mortem.

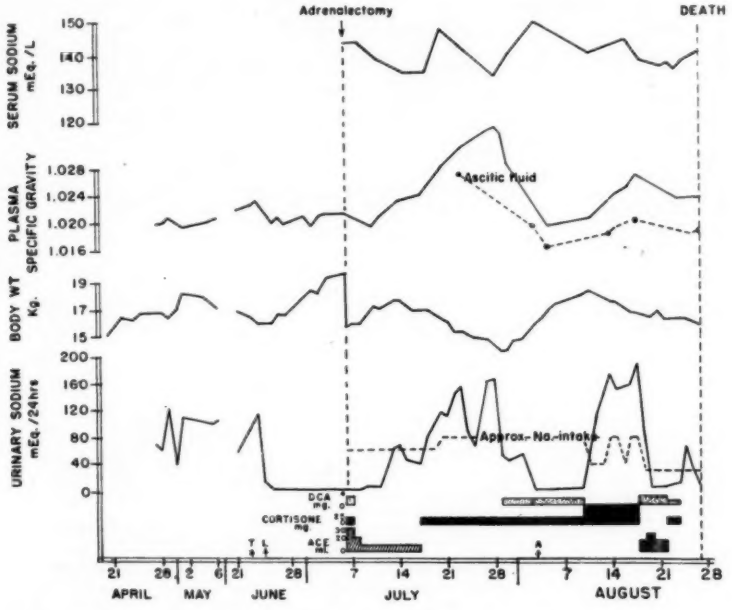

Fig. 8. Effect of adrenalectomy and substitution therapy in dogs with ascites from experimental mitral stenosis. (For details, see text.)

An attempt to produce diabetes insipidus in a dog already ascitic failed because of cellulitis and edema at the site of the operation.

To test the rôle of the adrenal gland, three animals were adrenalectomized on one side, the ligature placed and tightened until ascites appeared. One animal died. The other two became ascitic, and the second adrenal was removed. The first animal (Fig. 7) was treated for two postoperative days with whole adrenal extract, 25 cc. per day. When she was in good shape, extract was withdrawn and cortisone, 25 mg. per day was administered. What ascitic fluid had not been spilled during the operation was promptly evacuated and urinary sodium was markedly increased. The specific gravity of the plasma overshot, and then returned to normal. The animal was very vigorous. As soon as the ascitic fluid was gone, the plasma sodium decreased, the animal lost her appetite and showed other signs of adrenal deficiency. The cortisone was discontinued and she was given 10 cc. per day of whole adrenal extract (Upjohn). She came promptly into sodium balance and good health. Twenty cc. per day—four times the dose for normal adrenalectomized animals—did not cause any salt retention. Under the stimulus of mitral stenosis, the adrenal gland must have secreted an amount of the salt retaining hormone in excess of that contained in four maintenance doses of extract.

Cortisone treatment was then repeated. The animal again showed low plasma sodium levels and became ill. She was restored to vigor with a few doses of whole extract and maintained at that level with cortisone, 25 mg. per day and desoxycorticosterone acetate, 2 mg. per day. At autopsy the ligature was broken.

The second animal was adrenalectomized while in failure (Fig. 8). She was given 10 cc. per day of adrenal extract while she was still ascitic and came into approximate sodium balance without loss of ascites. Substitution of cortisone caused her to lose sodium and ascites in a profuse diuresis. The plasma sodium level remained normal and the animal vigorous as long as the store of ascitic fluid was available. When it was gone, the plasma sodium declined, and the animal became ill. Addition of desoxycorticosterone acetate, 2 mg. per day, put the plasma sodium back to nor-

mal and caused her to become vigorous again. The sodium excretion soon became minimal and the ascites returned. The desoxycorticosterone acetate was withheld, the cortisone dosage was increased to 75 mg. per day. The ascites was evacuated and the sodium excretion increased very much. The animal deteriorated at this point and died while we were attempting to improve the substitution therapy.

Conclusion

In concluding, it may be said that the mitral stenosis produced in these dogs resembles closely, in the size of the mitral orifice, and in the nature of the murmur, the condition seen in severe clinical cases. It leads to congestive failure (ascites) but this condition in the dog differs from congestive failure in man in that the fluid is collected in the abdomen rather than in the interstitial spaces. The effects of posture and gravity can be assigned a rôle in this difference.

The condition of our dogs lacks another of the usual signs of human congestive failure—*viz.* a high venous pressure. However, there are many clinical cases on record of cardiac edema with low venous pressure and many with high venous pressure and no edema.[1] Patients will gain or lose edema fluid regardless of whether their venous pressure is high or low if maneuvers are undertaken to correct renal errors in water balance.

The low venous pressure, and the absence of signs of passive congestion in the abdominal viscera, minimizes the rôle of possible forced filtration in these dogs. The amelioration of the ascites with sodium deviation by means of carbo-resin emphasizes the rôle of sodium in the disturbance. The fact that renal blood flow and glomerular filtration were not unduly restricted, indicates that the primary disturbance is a stimulation of the resorbtive function of the tubules.

The result of adrenalectomy implicates this gland and the fact that ascites would not increase under four times the maintenance dose of cortical extract implies either that the secretion of the gland was very excessive as a result of the stenosis, that the adrenal secretion was abnormal in character, having an undue amount of the salt retaining (amorphous) fraction or else that, in addition to the adrenal disturbances, there may be a disturbance in the function of the posterior pituitary.

Evidence that the pituitary is involved is very tenuous. If is only that the dog with experimental diabetes insipidus did not become ascitic under conditions that made other dogs ascitic. Further work is going on in an attempt to elucidate this problem.

It is interesting to speculate as to the rôle which this endocrine mechanism may play in health. Can it be decided whether we are working with a homeostatic mechanism that is being over stimulated, or an emergency response that is being continuously activated, either of which might lead to the vicious cycle seen here.

Gauer has presented evidence in this symposium that experimental procedures which tend to increase the effective local pressure of the blood within the great veins, right heart, and lungs, cause an increase in the output of salt and water. This is evidently a homeostatic mechanism. The stimulus, an increased distention of the low pressure blood reservoir, being the resultant, naturally, of an increase in the intravascular volume and the diuresis which eventuates, would decrease fluid and blood volume.

However, Gauer's mechanism is not the one that causes dogs with mitral stenosis to form ascites. Both the Gauer and the present procedure cause elevation of the effective pulmonary vascular, and right heart pressures. Gauer's dogs have diuresis; the mitral stenosis dogs have oliguria. It seems that we must think that the mitral stenosis dogs are making use of an emergency rather than a homeostatic mechanism. The oliguria of exercise,[30] which conserves salt and water, may be overstimulated and continuously activated until sodium practically disappears from the urine and ascites develops. The circulatory handicap may act like chronic exercise and set the mechanism off. The post pituitary is undoubtedly involved in the oliguria of exercise and may, perhaps, be over active here. An atypical stress reaction[24] may involve the adrenals. The picture is not clear and much further work should be done.

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COARCTATION OF THE AORTA

Coarctation of the aorta will vary from a partial narrowing of a considerable portion of the aortic arch to a severe localized constriction. Mild cases of coarctation will be asymptomatic and may be discovered only at necropsy. The chief clinical finding is *evidence of hypertension in the upper extremities* with decreased to absent pressures in the lower extremities, as manifested by faint or absent femoral pulsations. (Normally the pressure in the leg is greater than that in the arm.) Murmurs may or may not be present. The classic x-ray finding of notching of the ribs is rarely found before the age of fourteen years, as it takes time for the collateral circulation to cause pressure erosion of the ribs. Operation is indicated if the hypertension is severe or increasing.

The optimum time for surgery is under fourteen years of age because of the early appearance of arteriosclerotic plaques in the aorta, with consequent technical difficulties in suturing after excision of the narrowed portion.—From "Diagnosis of Congenital Cardiac Defects in General Practice," American Heart Association.

Laboratory Aids to Medical Practice

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LABORATORY DIAGNOSIS OF HEMOLYTIC DISEASE OF THE NEWBORN

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THE laboratory diagnosis of hemolytic disease of the newborn is usually based on the demonstration of four general requirements: (1) Rh incompatibility between mother and father; (2) maternal Rh antibodies for erythrocytes of the father's Rh type; (3) presence of maternal antibodies on the infant's erythrocytes and (4) objective evidence of increased destruction of the infant's erthrocytes.

Demonstration of Rh Incompatibility

Proof of Rh incompatibility between parents depends on the reliability of tests to determine the presence or absence of Rh factor in erythrocytes. In general, such tests are reliable. However, shortcomings in routine Rh testing do exist. Occasional batches of testing serum with low potency are obtained from manufacturers. Increased demand for serum and decreased production have caused dangerous shortage of supplies at times.

Errors in Rh testing sometimes are made because tests are performed too soon after transfusion of blood of unknown Rh type. Errors occur because abnormalities in the patient's serum proteins may affect the results. Such errors are less common in obstetric patients than in patients who have chronic and complicated illnesses, such as lupus erythematosus, leukemia or malignant tumors. The only obstetric patients in whom this error might arise are those recently recovered from primary atypical pneumonia who have autoagglutinins that might give false positive results in an Rh negative person.

The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

This is the twelfth in a series of editorial reports sponsored by the Minnesota Society of Clinical Pathologists and designed to foster closer relationships between clinicians and pathologists.

Demonstration of Maternal Antibodies

When the Rh factor was first discovered, antibodies could be found in only about half of the patients who had babies with hemolytic disease. Later, with the discovery that Rh antibodies differed from other antibodies, it became possible to increase the sensitivity of these tests so that antibodies could be found in 98 per cent of mothers who later had affected infants. At present, tests for antibodies have fallen into some disrepute because workers developed overly sensitive tests and reported antibodies in many patients who had normal babies. Also, faith was lost in the tests because it was found that the titer of antibody did not have the prognostic significance originally claimed for it. For example, increasing titers during gestation were not invariably associated with severely affected infants.

Methods of testing for antibodies at the Mayo Clinic have not been changed during the past six years; these methods have given satisfactory correlation between the presence or absence of antibodies and the occurrence of disease in the infant. The sole object of such tests should be the prediction of disease in the infant so that all necessary arrangements can be made for proper management at birth. The ideal time to do these tests is as late in gestation as possible and yet in time to make arrangements for handling the problem at birth.

Demonstration of Maternal Antibodies on the Infant's Erythrocytes

Maternal antibodies on the infant's erythrocytes usually are detected by the antiglobulin, or Coombs', test. Experience with this test indicates that when antibodies are found consistently in the mother results of the Coombs test at birth fre-

quently are positive and other evidence of hemolytic disease is found. Negative results are obtained occasionally when other evidence of disease is present. Thus, positive results indicate trouble but negative results may be misleading. The Coombs' test should not be relied on as a sole means of diagnosis but should be performed along with other tests to meet the fourth laboratory requirement for diagnosis of hemolytic disease, namely evidence of destruction of the infant's erythrocytes at birth or within the first 24 hours of life.

Demonstration of Hemolysis

The best indicator of abnormal destruction of the infant's erythrocytes is an increase of indirect serum bilirubin to values of more than 4.5 mg. per 100 ml. of serum obtained from cord blood. The next best test is a decrease in erythrocytes to less than 3,500,000 per cubic millimeter of blood and next an increase in the incidence of reticulocytes to more than 10 per cent and of normoblasts to more than 15 per cent.

Therefore, the following laboratory tests are ordered and obtained immediately on babies born of Rh negative mothers who have Rh antibodies: serum bilirubin (cord blood), test for Rh factor, antiglobulin test and counts of erythrocytes, reticulocytes and normoblasts.

Comment

The diagnosis of hemolytic disease of the newborn is sometimes made although all four requirements are not met. The pathogenesis in these cases is not fully understood. Some investigators explain these cases on the basis of ABO rather than Rh incompatibility. Thus, one theory assumes that natural anti-B isohemagglutinins in the circulation of a group A mother may traverse the placenta and react with B substance on or in the infant's erythrocytes, leading to their abnormal destruction.

Death from hemolytic disease appears to be closely allied to toxic effects related to sudden breakdown of erythrocytes. Therefore, treatment now is being directed mainly at immediate replacement of the infant's blood with normal blood when any evidence of increased destruction is present. Thus, the presence of clinical jaundice within the first twenty-four hours, confirmed by values for indirect serum bilirubin of more than 4.5 mg., is a positive indication for replacement transfusion. Replacement transfusion using 500 ml. of blood usually causes about 50 per cent reduction in the value for serum bilirubin. It also eliminates from the infant's circulation any sensitized erythrocytes that have not yet been destroyed. If values for bilirubin continue to increase and go above 20 mg., further replacement transfusion is done.

Summary

The most important and vital need for successful management of hemolytic disease is the detection of jaundice during the first 24 hours of life. The explosive suddenness with which the hemolytic process sometimes develops without warning evidence emphasizes the fact that no substitute exists for almost constant observation of newborns for the appearance of jaundice, confirmed by measurement of serum bilirubin. The appearance of jaundice is an indication for immediate treatment.

LYON LABORATORIES DEDICATION

The new Elias P. Lyon Laboratories which include laboratories for cancer and heart research among others, will be dedicated February 11 in ceremonies to be conducted at the Coffman Memorial Union, University of Minnesota. Featured speakers at the dedication ceremonies will include President J. L. Morrill speaking for the University of Minnesota, representatives of the Public Health Service, and Dr. M. R. Runyon, executive vice president of the American Cancer Society.

The Minnesota Division, American Cancer Society, which supplied a major share of the funds for the construction of the new laboratory building, will conduct a workshop for state volunteer cancer workers in the Hotel Normandy, Minneapolis, February 10 and 11. Speakers who will help bring cancer information up to date for the field workers will include Dr. Bernard Zimmermann, cancer co-ordinator, University of Minnesota, and Dr. David Anderson, Austin, president of the Minnesota Division, American Cancer Society. Dr. John Bittner will conduct a tour of the University's cancer research facilities and Dr. Claude Hitchcock will be in charge of cancer exhibits in Coffman Union.

The Dean's Page

THE CANCER DETECTION CENTER

Intensive clinical and basic research during the past several decades has failed to provide a simple, direct, method of diagnosing cancer. At the present time many avenues of approach to this problem are being explored in various medical centers. While we wait and hope, it is imperative that we exhaust the possibilities of known methods for establishing a correct and early diagnosis of malignant disease.

It is becoming more apparent that earlier diagnosis and immediate treatment are the most significant procedures by which real improvement in long-term cancer patient survival will result. In order that this may come about for larger groups of people, increased emphasis must be directed to precancerous conditions and suspicious lesions. It is essential that all members of the medical profession join actively in this effort. In truth, "Every Doctor's Office Should Become a First Line of Defense as a Cancer Detection Center."

"Cancer detection" carries a unique significance as compared with "cancer diagnosis." Diagnosis implies the establishment of the cause of symptoms existing in a given patient. "Detection," on the other hand, indicates the finding of malignancies, pre-malignant conditions, or suspicious lesions or in symptom-free patients undergoing periodic check-ups.

The Cancer Detection Center at the University of Minnesota was established five years ago to test whether it would be feasible to examine large numbers of asymptomatic people for the earlier detection of malignancies in all organs of the body. Other Cancer Detection Centers have dealt primarily with organs readily accessible to the examining physician. This Center has placed emphasis on internal organs. It is now possible to review this five years' work.

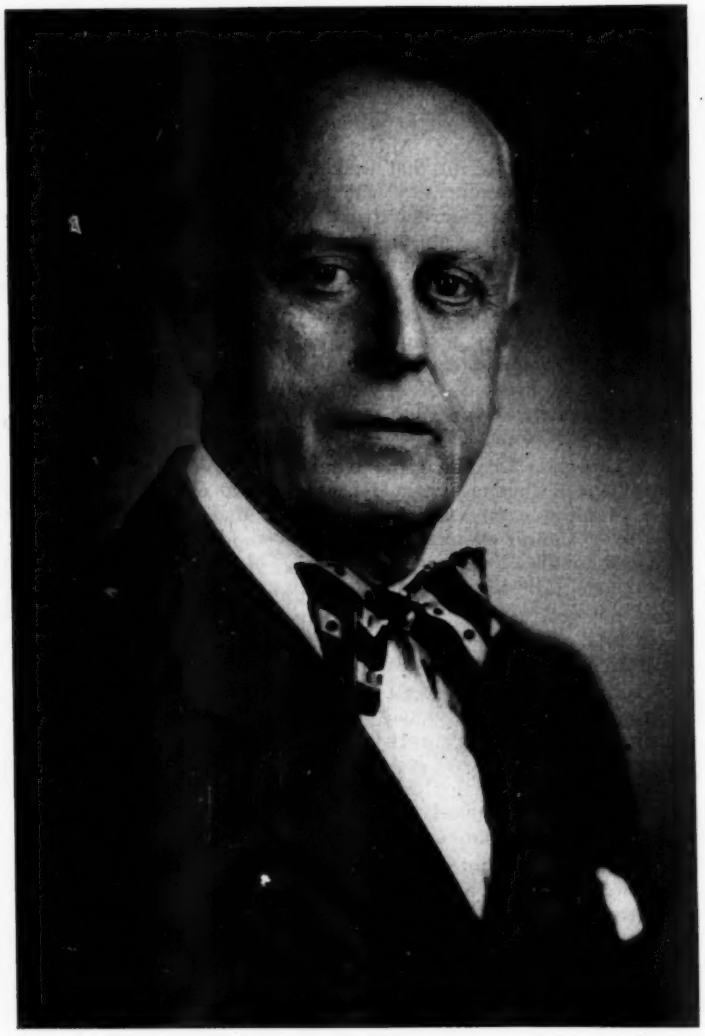
During this five-year period, 5,352 patients were given a total of 11,343 examinations. A total of ninety cancers have been found. Precancerous lesions were present in 1,300 of the examinees.

In spite of our efforts to do so, it has been impossible to limit examinations at the Detection Center to individuals completely free of symptoms. We have divided, therefore, our cases of cancers into two groups: those with some symptoms referable to the organ or organ system in which cancer was found, and those who were without symptoms for the organ or organ system involved. On this basis, cancer has been diagnosed in forty-four patients with symptoms and in forty-six patients without symptoms.

An immediate point of interest was whether there has been a significant difference in the survival of patients who had lesions detected in the absence of symptoms as compared with those who had symptoms which, in all likelihood, would soon have taken them to their family physician. In the gastrointestinal tract, including the stomach, large bowel, and rectum, there were twenty-nine cancers diagnosed. Ten of the lesions were in persons with symptoms and nineteen were in persons free of symptoms of gastrointestinal disease. At the present time, there are only two survivors in the group with symptoms of gastrointestinal disease, while fifteen of the asymptomatic group of patients, are living and well. All of these patients received therapy through customary channels of medical practice throughout the state of Minnesota. It appears that the most significant factor in the difference of survival has been the early diagnosis of the lesions in the asymptomatic phase of the disease.

The Detection Center at the University Hospitals has used a routine, comprehensive type of complete examination composed of standard diagnostic practices. We have found achlorhydria or extreme hypochlorhydria to be an accurate aid in selecting patients who should have gastrointestinal x-ray examinations. The proctosigmoidoscopic examination of the rectum and sigmoid has been extremely

(Continued on Page 53)



JUSTUS OHAGE, M.D.
President, Minnesota State Medical Association

President's Letter

NEW YEAR, NEW CENTURY

It is with great pleasure that I begin the year as president of the Minnesota State Medical Association. I am honored to have been chosen to represent the medical profession of Minnesota in the highest position its organization can confer on a doctor.

Traditionally, the office of president of the state medical association has carried with it the esteem of medical men in the state, the inherent dignity of any such position of leadership, and the dedication and selflessness of the men who have held the position in the past.

The men who have preceded me as president have exuded those qualities in great measure; they have been exemplary figures representing the purposes of medicine; they have deserved the trust placed in them by their colleagues; and they have been able leaders, strong and forthright in their beliefs.

With such an inspiring tradition, I pledge myself to carry on their noble ideals, for I have a deep respect for their work and for the profession's central purpose—to promote the science and art of medicine; to elevate the standard of medical education; and to promote public health.

Furthermore, 1954 marks the beginning of a new era for the Minnesota State Medical Association. With this year we are inaugurating a new century of medical organization in the state—having celebrated the centennial milestone last year.

Thus, I feel doubly proud to head this fine organization as it embarks on its second century of vigorous existence. What this new century will bring, none of us can tell. But one thing is certain: the underlying strength of the profession will increase its stature, broaden its outlook, and spur it on to even greater accomplishments.

During the coming year, I intend to work with the profession in Minnesota to bring that ideal one step closer. Working together with Association committees, the Council, the county medical societies, the House of Delegates and individual members, we shall make continued forward progress as an organization.

Thus, it is an honor and privilege for me to serve the medical profession of the state as its president. In spite of probable setbacks and pitfalls, with such a fine organization as ours, one cannot help but see that improvements will be forthcoming, and achievements will be more numerous.

President, Minnesota State Medical Association

Editorial

Arthur H. Wells, M.D., *Editor;* Henry G. Moehring, M.D., and John F. Briggs, M.D.

BOARD OF EDITORS

THE COUNCIL created a Board of Editors of MINNESOTA MEDICINE at its September session, and appointed ten members to the Board at the December meeting. This group is entrusted with the solicitation, selection, editing and publishing of scientific papers and news items of our journal. The organization and its functions appear in certain respects to be unique. Each member has specific and indispensable editorial duties.

Acting on the theory that one of the principal functions of the State Medical Association journal is to help develop self-expression and professional authority within the state, Dr. Glenn J. Mouritsen of Fergus Falls will seek out desirable scientific presentations in the county and regional medical society meetings throughout the state. A second Scientific Assembly Editor, Dr. Tague C. Chisholm of Minneapolis will cover meetings of state-wide medical organizations and those in the Twin Cities. Dr. L. E. Steiner of Albert Lea will edit a Business Assembly Section of the journal. Drs. Henry G. Moehring of Duluth, and John F. Briggs of Saint Paul will be responsible for the Editorial Section. Miss Olive V. Seibert, the publishers' editor, will represent a fundamental link with the Bruce Publishing Company. Dr. Alex E. Brown with Dr. George Stilwell, of Rochester, and Dr. Robert B. Howard with Dr. Stuart W. Arhelger, of Minneapolis, will represent the two great scientific fountains of our state. Among other things, they hope to develop a section of the journal which will compare with the popular brief reviews of several commercial magazines. Their slogan is "MINNESOTA MEDICINE, the Bedtime Companion of Every Physician."

Any alterations in the editorial organization or the published journal are not to be considered as criticisms of the past, but are based on the theory that a trial of variations in all of man's activities is essential to progress. Please keep in mind that the standing of a state medical journal is principally limited by the professional attainments and support of the membership.

CARDIAC SYMPOSIUM

THE scientific section of MINNESOTA MEDICINE in the January and February issues will be devoted to the presentations of the Symposium on Recent Advances in Cardiovascular Physiology and Surgery, held at the University of Minnesota on September 15, 1953. This meeting of outstanding authorities from the scientific centers of the world was made possible through the unusual efforts of Dr. Grace M. Roth, Dr. Robert B. Howard, Dr. John F. Briggs and many other physicians of our state and by the financial support of the Minnesota Heart Association.

You can keep up-to-date by reading MINNESOTA MEDICINE.

FORECASTS

THE first month of a year is the time for giving that year a prognosis. Some people call this forecasting and make it a favorite sport during January. From our friends, we have gleaned some general rules about these forecasts; to wit, (1) If you want to be spectacular, go ahead and make definite predictions about our economic future, the outcome of the next elections, or whatever you prefer to forecast about. But don't forget that we herewith advise you to limit your forecast to several paragraphs which commit you to nothing—the type of verbose ambiguity which sounds good, but actually boils down to an incongruous jumble of irrelevant considerations. (2) On the other hand, when the accuracy of your comments cannot be questioned, be (and in this connection we use the word with fear and only after fasting) precise. A known statistic or one that can't be checked should be quoted to the last decimal place, not rounded off to an easily remembered number; for example, reports of 1880 showed 275,545 cows in the state of Minnesota.

Our Forecast.—Some experts are predicting that the outlook for 1954 is as glum as a bad mistake. We don't hold with that. Adjustments will occur, surely, but in proper perspective, a moving

economy and society require such healthy changes. People will continue to try to get something for nothing, but will gradually become enlightened enough to settle for getting the highest quality something for the lowest price. And if physicians continue a patient and kindly program of enlightening the public about how to get the best medical care for the lowest cost to society, the year's end should show a real gain for the medical profession in the eyes of the public.

H.G.M.

MEDICAL CARE OF DEPENDENTS OF THE ARMED FORCES

When peace is gone and war is nigh,
God and the soldier is the cry.
When war is o'er and peace perfected,
God and the soldier are neglected.

THIS quatrain, so old it must be classed as "traditional" or "anonymous," touches on basic considerations in making up one's mind about medical care for dependents of those in the Armed Forces. It is recalled by the report from the Washington Office of the American Medical Association that a committee of admirals and generals recommend more medical care of dependents.

The report says a five-man committee believes that a serious deterioration of career service can be halted only by such things as higher military pay and more medical and dental care for dependents. Further, Assistant Secretary of Defense John Hannah warns that the services are losing career men in numbers "so great as to be disturbing." Secretary Hannah also cites low military pay and a "continual nibbling away at fringe benefits."

The immediate reaction may well be that military pay is already too high; as are taxes. What with this high military pay, why can't members of the Armed Forces pay for medical care like civilians? Well, we can only urge to look at the other side of the coin before you make any decisions:

If military pay is too high, why was, and is, everyone so eager to get out of the services into civilian life "where you can really make some money?" The fact remains that desirable members of the Armed Forces are leaving the services because pay is not high enough. Patriotism, loyalty to a cause, a high sense of duty—these are all well and good as statements of ideals, but day-in-and-day-out pay scale and benefits cut a more realistic and tangible figure to anyone objectively evaluating the pros and cons of making the Armed Forces his career.

The response that the "regulars" are no good anyway requires little rebuttal. One of the reasons that some career service men gave a poor impression during World War II was that the pay scale had been adequate for those men; their competence was a reflection of the pay scale rather than the pay scale's being a result of their ability.

You can't pick and train first rate chiefs of staff, surgeons general and top non-commissioned officers from a crowd of second rate men. You can't expect the crowd from which you intend to pick top-ranking career service men to be anything but overloaded with second raters if you don't pay them adequately.

It's the old story—you get what you pay for. If you want top quality men forming the "regular" framework of the Armed Forces, you must either pay for superior ability or put your hope and trust in finding a group of idealists who are above anything as mundane as pay and benefits.

H.G.M.

THE CANCER DETECTION CENTER

(Continued from Page 49)

valuable. Seventeen per cent of our examinees (all of whom are aged forty-five or over) have had adenomas or polyps of the rectum and lower sigmoid. Among patients who are asymptomatic the determination of occult blood in the stool has not been worth the laboratory expense and effort entailed. Careful visual examination of the vagina, and cervix, and bi-manual palpation of the pelvis have been rewarding in finding female pelvic malignancies. Five ovarian carcinomas have been detected and all were localized and confined to the ovary at the time of surgery. These women are all well at this time.

For the general public, the practicing physician is and always will be the key person in the diagnosis of cancer. A most important aspect of the Cancer Detection Center program is the evaluation and standardization of procedures which can be applied by physicians generally. We believe that physicians should continue to strive for wider application of cancer detection examination plans. Our Cancer Detection Center is eager to cooperate with them in so doing.

HAROLD S. DIEHL
Dean, Medical School,
University of Minnesota

Medical Economics

Edited by the Committee on Medical Economics
of the
Minnesota State Medical Association
George Earl, M.D., Chairman

IMPORTANT ACTIONS TAKEN AT AMA SESSION

The House of Delegates of the American Medical Association, meeting at the Jefferson Hotel in St. Louis, during the Seventh Annual Clinical Session, took important policy actions on social security, voluntary health insurance, medical ethics and unethical practices, medical education, hospital accreditation, military affairs and a wide variety of subjects affecting both physicians and the public.

G. P. of the Year

Highlight of the opening session of the House on December 1 was the announcement that Dr. Joseph I. Greenwell of New Haven, Kentucky, had been selected as the 1953 "General Practitioner of the Year."

The first day of the meeting also featured addresses by several Association officers, and annual reports from the Board of Trustees, the Secretary and General Manager and by standing and special committees of the House.

Compulsory Coverage Hit

Approving a recommendation by its Reference Committee on Legislation and Public Relations, the House passed a resolution reaffirming its opposition to the compulsory coverage of physicians under the Old Age and Survivors Insurance provisions of the Social Security Act, and advocating passage of the Jenkins-Keogh bills now pending in Congress. These bills were described as providing for "the development of a voluntary pension program which is equitable, free from compulsion, and satisfies the retirement needs of physicians."

The reference committee report adopted by the House said:

"The purpose of these bills is to eliminate the discrimination, and inequities which exist under present tax laws by extending the tax deferment privilege to the country's ten million self-employed and also to millions of employes who are not covered by pension plans. The purpose of the resolution is to reaffirm our support of the voluntary pension program provided in the Jenkins-Keogh bills and to reaffirm our strong opposition to the extension of compulsory coverage of physicians and other self-employed persons under Title II of the Social Security Act."

Bricker Amendment Supported

The same committee report urged continued action to obtain passage of the Bricker Amendment (S. J. Res. 1) and approved the principle of legislation which would reduce or remove the limitation on the deduction of medical and dental expenses for income tax purposes. The Bricker Amendment would outlaw any treaties which supersede the Constitution of the United States. The report also opposed any further extension of the "Doctor Draft" Law beyond the present expiration date of June 30, 1955.

On the "Doctor Draft" Law, the report stated that "your Committee feels strongly that there should be no further extension of the 'Doctor Draft' Law. We feel that the legislation is discriminatory and urge the Committee on Legislation and the Board of Trustees to actively oppose any further extension." AMA had recommended that the law be extended for only one year, when it expired on June 30, 1953.

Health Insurance Discussed

The House acted to accelerate the development of voluntary health insurance by passing a resolution requesting the Council on Medical Service to proceed immediately with a special study of the problems of catastrophic coverage and coverage for retired persons. The Council was asked to present its findings and recommendations to the House not later than the 1954 Clinical Meeting. The resolution pointed out:

"There are two large groups of citizens for whom improved coverage could be offered under present pre-

paid medical care plans, namely: (a) those individuals who suffer catastrophic or long-continued and highly expensive illness and whose financial resources are not adequate to meet the cost thereof and (b) those citizens who have retired and are living on small incomes and who are not eligible under presently existing public or private plans."

The resolution emphasized the medical profession's "responsibility to make every effort to promote such prepaid medical coverage for all citizens whose circumstances make them eligible."

Another resolution on voluntary health insurance, adjudged to be emergency business by the Reference Committee on Insurance and Medical Service and then passed by the House, stated that "the American Medical Association condemns all insurance contracts which classify any medical service as a hospital service."

The resolution was the result of information received that Health Service, Inc., a capital stock casualty insurance company owned by the national Blue Cross Commission, had issued insurance contracts containing medical benefits as well as hospital benefits, to employes of the meat packing industry on a national basis. The resolution stated that this was in violation of principles set forth by the House which define pathology, radiology, anesthesiology and physiatry as medical services.

A further statement in the resolution said: "this continued disregard becomes even more disturbing in view of the fact that Medical Indemnity of America, Inc., an insurance company said to be owned and controlled by Blue Shield Medical Care Plans, Inc., and Health Service, Inc., are operated under an agreement whereby each insurer assumes half of the risk underwritten by the other."

Ethics' Problems Studied

A resolution introduced by the Iowa State Medical Society, calling for approval of a joint-billing procedure involving services rendered by two or more physicians, was referred to the Judicial Council, at the suggestion of the Reference Committee on Miscellaneous Business, with the recommendation "that the Judicial Council investigate the factors involved in the matter as presented and determine if there are new factors or new facets that would cause it to change the opinion" determined in 1952.

In an effort to solve the publicity problems resulting from unethical practices by a small minority of doctors, the House referred to the Board of Trustees a resolution calling for appointment of a special committee with broad professional representation to study all aspects of the problems. The Board was asked to study and implement the intent of the resolution and to report its findings to the House at the June, 1954, meeting in San Francisco.

Dues Picture Clarified

Because of confusion on AMA dues which has resulted since the House began the practice several years ago, the delegates passed the following resolution, which clarifies the situation considerably:

"RESOLVED, that any active member of the American Medical Association who failed to pay dues for the year 1950, and who was suspended for such delinquency, may be reinstated during the first six months of 1954 by the payment of 1954 dues only.

"Should such an individual fail to pay his 1954 dues by July 1, 1954, he shall continue to be considered delinquent."

This resolution was substituted for one on the same subject which was introduced by Minnesota's delegates in June, 1953.

To clarify misunderstandings among physicians regarding the rules and regulations of the Joint Commission on Accreditation of Hospitals, especially as they concern the role of the Department of General Practice in a hospital, the House adopted the following resolution:

"That this House of Delegates of the American Medical Association request the Joint Commission on Accreditation of Hospitals to publish an article, or series of articles, in the *Journal of the American Medical Association* and other official publications circulating among the medical and hospital professions, to acquaint the medical-hospital profession with the regulations, by-laws and their interpretations, and

"That the Commission clarify the methods by which an aggrieved hospital or its staff may appeal a decision with which they are not in agreement."

Education Fund Bolstered

The House was "pleased to note" that a fourth grant of $500,000 had been made by the American Medical Association to the American Medical Education Foundation for financial aid to the nation's medical schools. The Foundation reported that its 1953 income now totals $1,174,000 and that the number of contributors is now more than double the total in 1952.

Dr. Louis H. Bauer of New York, immediate

past president of the AMA, was elected president of the Foundation just prior to the opening of the Clinical Session.

PR CONFERENCE DRAWS MANY

The Public Relations Conference, held the day before the Clinical Session of the AMA in St. Louis, was well attended by doctors interested in public relations and medical society personnel from all over the country. Those present heard many interesting and informative discussions on such topics as making a PR program work, what motivates the public's feelings toward medicine, selling the American economic system and how others do it, and mending PR fences.

One of the many talks presented that day was one by Mr. Roger Fleming, Secretary-Treasurer of the American Farm Bureau Federation. Mr. Fleming spoke on how the American Farm Bureau Federation informs the public about its program and its position on price controls.

He emphasized that simply because an organization happens to have taken a negative position on a matter, there is no reason to be ashamed and defensive about it. Illustrating, he stated that one of the most effective "programs" of all time has been the Ten Commandments, and that seven out of the ten begin with "thou shalt not."

Mr. Fleming also pointed out that Paul Revere and the rest of the early Americans were against something—they were against anything that was against freedom. "And that is the position of the Farm Bureau," he stated.

In conclusion Mr. Fleming sited the simile of the fruit growers in a certain state spraying their apples to prevent coddling moths from devouring them completely. It was not a matter of disliking moths so much, he stated, as it was a matter of liking apples so well.

FEDERAL SCHOLARSHIP LEGISLATION READY

The Defense Department's draft legislation for medical and other federal scholarships has received final checking over before presentation to the Budget Bureau for approval, according to a recent issue of the AMA Washington Letter. Budget Bureau approval is necessary if the plan is to be presented as an administration bill, but regardless of the bureau's action, the proposal could be offered by any member of Congress.

The plan provides:

1. Any medical, dental, nursing, or veterinary student accepting a scholarship would be obligated for one year of federal service for each scholarship year.

2. Payment would be made directly to the schools for tuition and other incidentals and to the student to cover living expenses during the school year.

3. Scholarships, limited to four years, would not be offered to pre-medical students or others preparing for professional courses.

4. Deans would make recommendations, but final selection would be by the Defense Department.

Department spokesmen explain that there are two objectives of the plan: first, to meet armed forces' needs after expiration of the doctor draft in 1955, if the regular draft obligation does not produce enough officers. Second, to interest enough young officers in regular military careers to maintain the regular corps at the necessary level. Currently regular medical officers make up only about 25 per cent of the medical corps total; it is hoped to reverse this ratio.

In regard to these federally subsidized scholarships, the AMA House of Delegates, at the Clinical Session in December, considered an emergency resolution which would have endorsed the principle of the scholarships. The resolution was discussed by a House reference committee, which recommended that the matter be referred to the Board of Trustees for study and action. The delegates approved this action unanimously.

HEPATITIS INCREASING

Infectious hepatitis (jaundice) is increasing in Minnesota as well as throughout the United States. To mid-December, 1953, 875 cases had been reported to the State Department of Health. Apparently no part of Minnesota is free from the disease, but it has been reported more frequently from some areas than from others. This difference may represent better reporting by physicians in the areas from which most cases are reported.

Early symptoms of infectious hepatitis include fever, nausea with or without vomiting, loss of appetite, fatigue, lassitude, headache, and abdominal discomfort.

Gamma globulin is reported to be effective in preventing infection in contacts where there is prolonged exposure. The Minnesota Department of Health supplies this material in limited quantities for family contacts of cases. A comparatively small dose is required for this protection—From *Minnesota Health*, January, 1954.

History of Medicine In Minnesota

MEDICAL HISTORY OF THE COUNTY OF YELLOW MEDICINE

MILDRED B. LEE
Granite Falls, Minnesota

(Continued from December, 1953, issue)

John Thomas Gill was born February 26, 1858, at Monroeville, Ohio, the son of Edward and Esther (Young) Gill. His father was a native of the Isle of Man, and had followed the trade of ship's carpenter. He had also helped in surveying the first railroad to be built on the Isthmus of Panama. Esther Gill was a native of Ohio.

John Thomas Gill was the fifth child in a family of nine children, and attended the public schools of Monroeville, Ohio. On completing his high school course he entered Western Reserve College at Cleveland, Ohio, then went to New York Medical College for his medical training, graduating in 1886. Two brothers, William and George, and a sister, Mary Gill, also chose medicine as a profession.

After receiving his degree in medicine Dr. Gill returned to Monroeville where he practiced medicine for four years. At the end of that time he went to Kansas City and practiced for a time in connection with the Cherry Street Hospital there. Following this experience he practiced in Chicago for two years. In 1895 he decided to look for a location in the west, and with Appleton, Minnesota, as his destination he chose a route through Yellow Medicine County over the Minnesota and St. Louis railroad. It was midwinter, and when the train reached Echo it was stalled by blizzard which tied up all rail traffic in the area. The passengers secured what accommodations were offered by the tiny settlement, Dr. Gill securing a room at the Nicollet House.

Word that a doctor was in town soon spread throughout the community, and before many hours had passed Dr. Gill was sought out by a man who was the father of two very sick children. At the farm home Dr. Gill found two little girls ill with diphtheria, one already beyond his help; from that time on Dr. Gill was in constant demand, and by the time the epidemic of diphtheria was past he had made up his mind to remain in Echo.

On October 9, 1896, Dr. Gill was united in marriage with Blanche McClure, who was a native of Seaforth, Ontario, Canada, but had been in Yellow Medicine County since 1894. After their marriage they resided in a small frame house in the business district of Echo and he had his office there for many years.

In appearance Dr. Gill was a slender, wiry, small-boned man of medium height with dark hair and dark eyes which were his most arresting feature. He was friendly, soft-spoken, but nevertheless a man of strong convictions; quick in his movements, decisive in action. His manner was unassuming, quiet, and kindly. He was everybody's friend, devoted to his patients, maintaining a high standard of medical practice and at the same time finding opportunities to take part in civic affairs for the betterment of the community.

In the course of his life in Echo he served as a member of the village council,

and as a health officer, and as a member of the school board. He also became a member of the Masonic Order.

Dr. Gill never refused a call. In his first years in Echo he hired a livery rig to take him on his country calls. Later he had his own team and buggy or cutter, and when automobiles came into general use he became the owner of a small car. Thus equipped he would brave any kind of weather, at any cost to himself, and often his pay for this gruelling service would be in the form of a quarter of beef, a load of wood, a dressed goose, or just a word of thanks. Dr. Gill had great sympathy for the needy; he gave freely not only of his medical skill but of whatever he could of material help. Many times Mrs. Gill and her daughters made baby clothes and bought infant's shirts for some needy expectant mother. His daughter Dorothy says, "I can still see him going off with a bundle of baby clothes under one arm, and a toy for an older child in another. He taught his own children that to get the most out of life you had to share with your neighbor. He personally loved every baby he delivered, and there were hundreds of them."

Dr. Gill was, in his quiet way, intensely patriotic. At the beginning of World War I he took an active part in arranging patriotic meetings. His son, Edward, was one of those who were killed in action in that war, and brought home for burial in native soil.

As the years passed, nine children were born to Dr. and Mrs. Gill, grew up, and were educated in the local schools. As Dr. Gill grew older there was no slackening of his efforts to take care of the health problems of the community. During World War I he bought a house in Echo which he equipped as a sort of hospital, or nursing home, for his patients. In later years he took many of his patients to Redwood Falls Hospital. His daughter Esther became a nurse, the only one of his children showing his own inclination to service in the field of medicine.

In February, 1938, some of the people of Echo undertook to make a public show of appreciation for the doctor who had served them so tirelessly and devotedly for forty-three years. They planned a surprise party of grand proportions to be held at the auditorium on a Sunday afternoon, with a suitable gift to be presented to the guest of honor. But on February 21 Dr. Gill received a call from a country patient. Unable to locate his son Robert, who now drove for him, he decided he would go alone, as the Koecher home to which he was called was only two miles from Echo. He reached the home, attended to the needs of his patient, and started back again in his little car. The roads were partially blocked with snow, and Mr. Koecher therefore followed the doctor's car with team and wagon to see that he got safely through the bad places in the road; and when the car stalled he went to help the doctor put additional "snow links" on the wheels. Mr. Koecher had finished putting them on one side, then walked around the car to find the doctor lifeless in the snow.

It was found that death came as a result of a heart attack.

The doctor was survived by his wife and seven children. One child, a son, had died in infancy; Edward was killed in the first World War. The children surviving were James, Crystal (Mrs. P. E. Long), Margaret (Mrs. Fred Norton), Almona, Robert, Esther, Dorothy (Mrs. Carl Sorenson); also eight grandchildren.

The following obituary appeared in the February 25 issue of the *Echo Enterprise*, of Echo, Minnesota.

JOHN THOMAS GILL

His Death Came Suddenly, Without Warning,
Taking from Us Our Best Beloved Citizen.
The Entire Community Mourns.

Our village was stunned and shocked on Monday when word flashed around town that our best beloved citizen, Dr. John T. Gill, had suddenly passed away while making a call to the Fred Koecher home two miles southwest of Echo. The doctor was very busy that morning, and not being able to locate his son, Robert, when ready to start, decided to make the short drive alone. He had reached the Koecher home but before starting back they had placed two snow links upon each of the wheels. Mr. Koecher accompanied the doctor but just before reaching the highway 67 the car stalled. The two men got out to put an extra link upon the wheels. Mr. Koecher had got his link on and upon walking around to the other side of the car saw the doctor slumped over, dead.

Mr. Koecher who had followed the car with his team was obliged to drive back home to summon his son, Fred, Jr., who in turn contacted Alfred Bode and Robert Gill and drove to the scene of the trouble.

The hearse was then secured and the body brought to the mortuary rooms.

The doctor, as the most familiar figure in Echo over this wide span of years, will be sadly missed. Throughout his long residence here as a country doctor he had always stood ready, in all kinds of weather, to answer sick calls and administer to the need. He alone had visited more homes than any other resident, and was always on hand when needed. We join with citizens in general in paying just tribute to this worthy man and doctor. His will be a link in the lives of Echo citizens that will be hard to fill.

In the early days when this country was sparsely settled, and it was necessary to make long trips over the prairie, even in the winter time, with a cutter or bob sled, he never refused to respond to a call.

John T. Gill was born at Monroeville, Ohio, February 26, 1858, where he grew to manhood. After finishing the high school course in his home town, he attended the Western Reserve College at Cleveland and the New York Medical College at New York, graduating in 1886. He returned to his home town and practiced four years. He then went to Kansas City, Missouri, and practiced two years in the Cherry Street hospital. After two years in Chicago he came to Echo in 1895, where he has practiced his profession for the past forty-three years.

Dr. Gill was married October 9, 1895, to Miss Blanche McClure, the ceremony taking place at Redwood Falls. Mrs. Gill came to Echo in 1894 from Seaforth, Ontario, Canada. The widow and seven children survive, namely, James, Mrs. P. E. Long (Crystal) and Mrs. Fred Norton (Margaret) all of Minneapolis, Almona and Robert of Echo, Esther of Detroit, Mich., Mrs. Carl Sorenson (Dorothy) of Tyler. Edward Gill was a victim of the World War, dying in France with burial in Echo cemetery. One son died in infancy. Eight grandchildren also survive. Dr. Gill was a member of the Masonic order. He had served on the village council and school board and was health officer. The parents of Dr. Gill were Edward and Esther Young Gill. The father was born in the Isle of Man, and the mother in Ohio. They passed away in 1920 and in 1912. Mr. Gill Senior was a ship carpenter by trade, and helped survey the first railroad on the Isthmus of Panama. John T. Gill was the 5th child of a family of nine children. Surviving brothers and sisters were Dr. Mary Hunter and Miss Ruth Gill, of Grand Junction, Colo., Miss Bertha Gill, Ypsilanti, Mich., Dr. William Gill, Norwalk, Ohio, Dr. George Gill, Elyria, Ohio, Ernest Gill, Redondo Beach, California. Three sisters preceded him in death.

Dr. W. R. Alexander, pastor of the Presbyterian Church at Vesta, will officiate at the service at one-thirty at the auditorium.

Edward Henry Kerkhoff was born on May 13, 1872, on a farm in Spring Hill Township in Stearns County, Minnesota, about eight miles from Melrose. He was the son of Conrad Kerkhoff who was a native of Lippstadt, Westphalia, Germany, and Catherine Horner Kerkhoff, a native of Stuttgart in Wurttemberg, Germany. The parents had come to the United States and settled first in Wisconsin, then in Minnesota. In 1884 they settled on a farm near Melrose and Edward attended school there. After finishing his studies he took up telegraphy, but about 1894 he made up his mind to study medicine, enrolling in the old Hamline University Medical Department (Minneapolis College of Physicians and Surgeons). He completed his studies and graduated in 1899, but he had been licensed to practice medicine on June 16, 1898.

Early in June, 1898, Dr. Kerkhoff went to Clarkfield with the intention of

locating there, as shown by the following announcement of the *Clarkfield Advocate*, on June 2, 1898:

"Dr. E. H. Kerkhoff came up from Minneapolis last Friday and is now permanently located in Clarkfield. The doctor comes very well recommended, is a very pleasant gentleman to meet, and we predict success for him in our midst. He can be found at the drug store or Commercial House for the present. For the benefit of those who do not speak English we will state that the doctor can converse in both Skandinavian and German."

At the time of Dr. Kerkhoff's arrival in Clarkfield there were two other doctors in residence there; Dr. Albert R. Torgersen, a pioneer physician of the county, and Dr. J. Woodbury Donnell who was county coroner and also county physician. Dr. Donnell was a single man, often depressed and moody. He drank heavily at times, and his manner was not one to inspire confidence. Consequently he was not very successful in establishing a practice in Clarkfield, and spent most of his time helping out in the drug store.

On June 16, Dr. Kerkhoff was asked to make a professional call upon Dr. Donnell. On arriving at the doctor's rooms over the Clarkfield Drug Store Dr. Kerkhoff found Dr. Donnell lying in bed, bleeding profusely from a wound in the throat which he had inflicted upon himself with a pair of scissors. He was also in the throes of convulsions due to a dose of strychnine, also self-administered. In an attempt to save Dr. Donnell's life Dr. Kerkhoff quickly summoned help and endeavored to sew up the wound in the throat, but the patient died within a few hours.

In November Dr. Kerkhoff decided to leave Clarkfield. The *Clarkfield Advocate* of November 10, 1898, announced:

"Dr. E. H. Kerkhoff left last Saturday for Minneapolis where he will enter the City Hospital for the purpose of improving himself in his chosen profession. During his stay in Clarkfield the doctor made many fast friends, all of whom will greatly miss him. It is hoped that he will again locate in this village when he has finished his hospital service."

After completing his internship at the Minneapolis City Hospital Dr. Kerkhoff was for a short time in Kasson, then in Plainview (Wabasha County). On December 19, 1899, he settled in Pierz, Minnesota, where he continued to practice until his death.

In 1904, Dr. Kerkhoff was married to Miss Rose Vorath, of Agram Township in Morrison County, near Pierz. There were two children born of this marriage.

In 1906 Dr. Kerkhoff practiced for a time in Richmond, Stearns County, but returned to Pierz within a few months. In addition to his medical practice he edited the *Pierz Journal* and was very much interested in farming.

Dr. Kerkhoff was known as a physician who was devoted to his patients and tireless in their service. He was exceptionally well read and interested in many fields outside the practice of medicine. His devotion to his patients caused him to continue caring for them during the pandemic of influenza which followed the first World War, although he himself had been ill for several weeks and was not well enough to resist the disease. He became ill with influenza, complicated by pneumonia, and he died in Pierz on November 15, 1918, at the age of forty-eight years.

John S. Kilbride, son of Michael and Mary (Quinn) Kilbride, was born in the village of Zwingle in Jackson County, Iowa, on December 23, 1865. His father and mother were born in County Roscommon, Ireland, where the Kilbride

family had lived for many generations and worked in the trades of weaving and spinning in the Belfast district. Mary Quinn Kilbride was born in County Mayo, Ireland. Michael Kilbride and Mary Quinn came to the United States as young people, and met and were married at Chilicothe, Ohio. After their marriage they moved to eastern Iowa, and then to Havana, Illinois. They came to Jackson County, Iowa, about 1865. Three brothers of Mary Quinn had been killed in the Civil War. In Jackson county the Kilbrides prospered, and they acquired a farm of four hundred acres. Four children were born to them, the oldest of whom was John S. Kilbride. Michael Kilbride died at an early age, when the children were small. Mrs. Kilbride married again, and the stepfather was highly esteemed and respected by the children.

John S. Kilbride grew up in Jackson County, living on a farm and attending country schools. He also had a course at the State Academy at Iowa City, then went to Minneapolis where he attended Central High School, working for his board and other expenses. In the summer he did farm work, or any kind of work he could get.

For his medical training Dr. Kilbride entered the University of Illinois School of Medicine in Chicago, and graduated in 1893. He began his medical practice at Dawson, in Lac qui Parle County, Minnesota.

In the fall of 1894, a pretty young woman by the name of Jennie Spragg came from Milwaukee to teach school at Dawson, and shortly became ill with pneumonia. Dr. Kilbride was called to attend her, and it soon became apparent that she was a very sick girl. Dr. Kilbride was determined to save her; he was almost constantly at the house, neglecting all other calls to devote his efforts to her recovery. His efforts were rewarded; not only did she recover, but she became his wife, the mother of four children: Stephen, who died in infancy, Edward A., Linnae, and Zylpha.

In 1897 Dr. Kilbride took additional medical training, then practiced for a short time in Sleepy Eye. In 1900, he located in Canby.

From the first years of his practice Dr. Kilbride showed exceptional skill and aptitude for the practice of medicine. In his first years at Dawson he earned a reputation for quick and correct diagnosis and treatment. An instance is related of a young man suddenly stricken with appendicitis; Dr. Kilbride lost no time, but operated on the patient on a kitchen table, and removed an appendix already ruptured; the patient recovered. Again, cholera morbus which had claimed many small lives in Dawson, was promptly treated by Dr. Kilbride with unfailing success. His devotion to his patients in that community is still gratefully remembered.

A misfortune that befell the second son, Linnae, in Canby, weighed heavily on the doctor's mind for many years. The railroad had a turntable at Canby; in legal parlance, classed as an "attractive nuisance" in that children were so often drawn to them as a playground. Returning from a professional call one evening the doctor espied his two young sons playing around, and he took them home, and warned the maid and their mother about letting them play away from home. Then he left for his office. Within a short time the little boys were out of the house and back at play; this time they ventured on to the turn table, and Linnae's leg was so crushed that it became necessary to amputate it. Dr. Kilbride was a man of deep feeling, Irish temper and temperament, and he never got over feeling that the accident should have been prevented.

Mrs. Kilbride died August 16, 1908.

Dr. Kilbride was a general practitioner, but he also was a specialist in eye, ear, nose and throat surgery and skin diseases. He kept up with all developments in

the field of medicine and attended clinics in medical centers both at home and abroad. In 1910 he went to Germany and studied for a year at the Zeugniss University, afterward touring Europe and visiting the birthplaces of his parents in Ireland. In 1911 he returned to Canby and sold his practice there to Dr. Field, then located in Watertown, South Dakota, where he practiced for four years.

During his residence at Watertown he married again, his second wife Marie being a former resident of Hastings, Minnesota. Of this marriage there was one child, a daughter, Kathleen. The second Mrs. Kilbride was a stately, handsome woman and a Catholic.

In 1915 Dr. Kilbride returned to Canby and formed a partnership with Dr. L. J. Holmberg. This association continued until 1936, when Dr. Kilbride sold his interest to Dr. Holmberg and went to Worthington to practice with his son, Dr. Edwin. In 1943 Dr. Kilbride returned to Canby and established an office in his home, and practiced until the end of World War II, when he returned to Worthington.

In December, 1949, he was severely injured in an automobile accident, and never recovered from it. As a result of his injuries he suffered kidney trouble with complications; loss of vision, and other difficulties. He was treated at Rochester, Minnesota, but rapidly failed and died May 26, 1950, at the Kilbride Hospital in Worthington.

Dr. Kilbride was survived by his four children, Dr. Edwin A. Kilbride of Worthington, Attorney Linnae of Hastings, Zylpha, wife of Stanford Clinton, an attorney, of Chicago, and Kathleen, wife of Nelton Knoop, of Des Plaines, Illinois.

Dr. Kilbride was a Democrat, a member of the Catholic church, and of the Holy Redeemers Council of the Knights of Columbus at Marshall, Minnesota. He was a member of the Minnesota State and American Medical Associations, and was at one time President of the Camp Release Medical Society. He was interested in agriculture, and owned several farms in Yellow Medicine County.

Dr. Kilbride's obituary appeared in the *Canby News*, June 2, 1950.

"Dr. John S. Kilbride, 84, physician and surgeon in Canby for 32 years, died in the Kilbride Hospital at Worthington Monday night.

Dr. Kilbride, who had been living with his son, Dr. Edwin Kilbride in Worthington since 1945, had been seriously injured in an automobile accident shortly before Christmas, 1949, sustaining a partial rupture of his stomach, and never fully recovered, and had failed rapidly recently. He had lost much of his vision before his death.

Funeral services took place at a Worthington funeral home this morning (Thursday) and burial was made in the Worthington cemetery.

Born in Iowa, December 23, 1864, he grew up in Dubuque and following his graduation from medical school began practicing in Dawson in 1898. After a year there he went to Sleepy Eye and practiced there for a year before coming to Canby in 1900.

In 1910 he went to Germany and studied for a year, and on his return sold his practice here to Dr. Field, and established an office at Watertown, South Dakota, where he practiced for four years. In 1915 he and Dr. L. J. Holmberg formed a partnership here which continued until 1936, when Dr. Kilbride sold his interest to Dr. Holmberg and formed a partnership with his son in Worthington. In 1943 Dr. Kilbride returned to Canby and established an office in his home and practiced until the war ended, returning to Worthington in 1945.

Surviving are four children; Dr. Edwin in Worthington, Attorney Linnae in Hastings, Zylpha in Evanston, Ill., and Kathleen (Mrs. Nelton Knoop) in Des Plaines, Ill."

Dr. Thomas McKey graduated from the Chicago Medical College in 1878. He then took a postgraduate course at the State University of Iowa City, Iowa, in

surgery, under Professor W. F. Peck. He completed his course and received another diploma from that institution in March, 1882.

Dr. McKay's medical practice was begun in Merrill, Wisconsin. He was appointed surgeon of the Waupun Prison in 1883, and remained there until 1885 when he moved to Luverne, Minnesota. After a residence of six months in that place he removed to Clear Lake, South Dakota, and practiced there for ten years. In 1896 he located at Canby, Minnesota.

Dr. McKey was a man of average height and very corpulent, weighing in the neighborhood of 250 pounds. He was a pleasant man to meet, friendly and jovial, and made many friends. He was considered to be a very good doctor and he enjoyed a good practice while in Canby. Both the Doctor and Mrs. McKey were very well liked, and they had several children. So far as is known they had no church affiliations in Canby, but Dr. McKey was one of the first officers of Cassiopea Camp, Royal Neighbors, organized in Canby in 1899.

Dr. McKey remained in Canby until after 1900, and then went to Albert Lea, Minnesota.

Dr. M. G. McLean. Nothing is known about Dr. M. G. McLean aside from the fact that he was located in Canby for a few years prior to 1881, and served as coroner in 1878. His period of residence covered about the same period as that of Dr. Billington but there are few who remember anything about him, and as there is no record of his practice it is possible that he was not a graduate with a medical degree. He was, however, recognized as a physician by the county board, which at its meeting in March, 1877, allowed a bill of Dr. M. G. McLean for $2.00 for medical attention to the poor.

Dr. McLean took into parnership Dr. Herman E. Farnsworth in 1880, and the firm is mentioned in Rose's History of Yellow Medicine County in connection with the case of Michael J. Dowling, victim of the storm of October 15, 1880.

James McPeek was born in Indianapolis, Indiana, on March 5, 1852. He was the son of Thomas McPeek, a native of Indiana, and Sahara Barto McPeek who was born in Maine of French Huguenot stock. The family removed to Olmsted County, Minnesota, about 1855 and settled on a farm near Byron, where the boy grew up and attended the public schools of the county.

On December 24, 1875, James McPeek married Miss Ruth Ann Stevens. Some years later he decided to study medicine, and enrolled in the Keokuk College of Physicians and Surgeons in Iowa, graduating in 1889. Following this, and possibly for some time prior to his graduation, he practiced medicine in Gary, South Dakota.

When Dr. McPeek decided to locate in Canby, Yellow Medicine County, there were five McPeek children: Maude, George, Earl, DeEtte, and Sadie. In the spring of 1891 Dr. McPeek purchased, in partnership with O. M. Eichinger, the Adolph Gilberson drug store in Canby, and moved his family into the O. N. Lund house. At this time Mrs. McPeek was in poor health, and accompanied by daughter Maude she went to the home of her mother at Owatonna. In October it was found that her ailment was incurable, and she died in January, 1892, and was buried at Owatonna.

For a time the McPeek family was broken up, some of the younger children being placed with relatives. During this period Dr. McPeek was away on business for the drug store and personal affairs demanded much attention, so his brother Dr. E. A. McPeek "from the eastern part of the state" came to Canby with the intention of remaining there permanently; but he stayed only a few months.

In the latter part of 1892, the drug firm of McPeek and Eichinger bought out the stock of Dorr and Jenson and consolidated the two businesses. This store was one of those destroyed in the great fire in Canby on September 5, 1893; also it was one of the very few to be insured.

Dr. McPeek continued as a member of the Board of Pensions which met in Gary, South Dakota. He had been licensed to practice in that state on May 25, 1889, and made frequent trips there; the older children also kept their connections there. On September 16, 1893, Dr. McPeek was united in marriage with Mrs. Bessie Eakins, of Gary, a widow who had a son by her former marriage. This boy joined the family at Canby and attended school there, and in 1894, a son was born to Dr. and Mrs. McPeek.

Dr. McPeek was in early middle age when he came to Canby, and was of medium height, inclined to fat. He was genial and likeable, a very friendly man. The second Mrs. McPeek was a woman of striking good looks.

About 1895 Dr. McPeek left Canby to locate at St. Charles, Minnesota. Thereafter he moved to Kasson, about 1898, and in 1899 he moved to Sleepy Eye in Brown County. In 1903 he was located in International Falls, where he became health officer of the town. In 1906 he returned to Gary. In 1912 he was practicing at Breckenridge and was the local surgeon for a railway company there.

In his later years Dr. McPeek lived at Ranier, on Birch Point, Rainy Lake, Minnesota. He died of erysipelas of the face at the home of his daughter, Mrs. Stephen Trageser, of Minneapolis, on December 24, 1922, and was buried at Byron, Minnesota.

(To be continued in the February issue)

RHEUMATIC FEVER AND THE SCHOOL CHILD

The school gives an unusual opportunity to attack rheumatic fever. Certain improvements in school health services are needed to make the best use of this opportunity. These recommendations of the Academy will not only be a better approach to rheumatic fever but to other health problems of children. The alertness of teachers and school nurses can bring to medical attention children with signs and symptoms suggestive of rheumatic fever whose condition might otherwise be overlooked. It is also an opportunity through periodic medical examinations to discover unrecognized damage to the heart and to keep under medical supervision known cases of the disease and to make family studies of rheumatic children. It is an opportunity to teach the principles of healthful living to children who have the disease or who are susceptible.

To aid school health authorities to develop a more rational approach in the control of disease, the Committees on School Health and Rheumatic Fever of the American Academy of Pediatrics recommend: (1) that the school medical examination be improved to aid in more accurate recognition and supervision of rheumatic children, (2) that more emphasis be placed on referral by teachers and nurses of pupils believed to be below-par for medical review, (3) that less emphasis be placed on restricting the physical activity of rheumatic children and more attention given to daily observation of pupils for signs or conditions suggestive of rheumatic disease, (4) that there be available, to school health services and the practitioners, diagnostic and consultation services to establish diagnosis, (5) that these services be developed in co-operation with, and by utilization of, existing medical and public health resources in the community. —From Report of the Committee on School Health and the Committee on Rheumatic Fever of the American Academy of Pediatrics, 1948.

THE MINNESOTA STATE BOARD OF MEDICAL EXAMINERS

230 Lowry Medical Arts Building
Saint Paul 2, Minnesota
E. M. JONES, M.D., *Secretary*

MINNEAPOLIS WOMAN MUST SERVE SIX MONTHS FOR ABORTION

Re. State of Minnesota vs. Annabelle Keith

On December 7, 1953, Mrs. Annabelle Keith, aged twenty-seven, 2805 St. Mary's Place, Minneapolis, was sentenced by the Hon. Theodore B. Knudson, Judge of the District Court of Hennepin County, to a term of not to exceed four years in the Women's Reformatory at Shakopee on an abortion charge, the sentence being stayed, however, and the defendant placed on probation on condition that she serve the first six months of her sentence in the Minneapolis Women's Detention Home. Judge Knudson further provided that Mrs. Keith should begin serving her term on December 29, 1953. The defendant had previously, on October 13, entered a plea of guilty before Judge Knudson to an information charging her with the crime of abortion.

Mrs. Keith was arrested by Minneapolis Police Officers on October 2, 1953, when it was discovered that she had aborted a twenty-four-old Saint Paul divorcee about three weeks previously. The defendant performed the abortion upon the patient who was three and a half months pregnant, by using a catheter and was paid the sum of $50.00 for her services. She is not licensed to practice any form of healing in this state and further admitted that she has had no medical training but claimed to have learned how to do abortions from a Milwaukee, Wisconsin, woman in 1942.

ONE MINNEAPOLIS MAN GIVEN PRISON TERM, ANOTHER PROBATION FOR ABORTION

Re State of Minnesota vs. Paul Schwede and Julius J. Capra

On October 1, 1953, Paul Schwede, forty-nine, 127 West 26th Street, Minneapolis, a meat market operator, was sentenced by the Hon. Theodore B. Knudson, Judge of the District Court of Hennepin County, to a term of not to exceed four years at hard labor in the State Prison at Stillwater for the crime of abortion. Because he was not placed on probation Schwede must serve his sentence

On November 9, 1953, Judge Knudson sentenced Julius J. Capra, thirty-five, a meter reader who resided at 239 Clifton Avenue, Minneapolis, to a three-year prison term on the same charge, the sentence being suspended, however, and the defendant placed on probation for the same period.

Both defendants were arrested in connection with the same case. An investigation disclosed that Capra had given the name and phone number of a twenty-eight-year-old Minneapolis divorcee who was seeking an abortionist, to the defendant Schwede. The abortion was later performed by Schwede, who holds no license to practice any form of healing in Minnesota. Of the $285 that was paid for the abortion Schwede received $200 and Capra was paid $85 for his services in the case. The investigation revealed that Capra had referred other women to Schwede for the same purpose in the past.

The defendant Schwede has a previous conviction for abortion, having been sentenced on June 20, 1950, by the Hon. Rolf Fosseen, Judge of the District Court of Hennepin County, to a term of not to exceed four years in the State Prison at Stillwater on that charge. However, the sentence was stayed for three years and Schwede was placed on probation after he had served three months in the Minneapolis Workhouse. The records of the United States District Court in Minneapolis disclose that on November 4, 1946, Schwede was fined $200 following a plea of nolo contendere to an information charging him with a conspiracy against the United States in connection with the illegal use of counterfeit sugar stamps.

MINNEAPOLIS WOMAN SENTENCED FOR ABORTION

Re State of Minnesota vs. Lois Townsend

On October 30, 1953, the above-named defendant was sentenced by the Hon. Theodore B. Knudson, Judge of the District Court of Hennepin County, to a term of not to exceed four years in the Women's Reformatory at Shakopee on an abortion charge, the sentence being stayed, however, and the defendant placed on probation for the same period of time. She had previously on September 16 entered a plea of guilty before Judge Knudson to an information charging her with that crime.

Miss Townsend, twenty-nine, was charged with having taken medicine, drugs or other substances, and used certain instruments with intent to produce her own miscarriage. She was brought by ambulance on August 21, 1953, from her apartment at 1325 Hawthorne Avenue, Minneapolis, to General Hospital because she was hemorrhaging as a result of an abortion, which medical opinion held to be an induced abortion.

When the police searched Miss Townsend's apartment, they found a bone knitting needle, which had the appearance of a catheter, some quinine, and also a wire such as those that are inserted inside of catheters. In addition they discovered a medical book that had a marker in it on a page which dealt with the subject of abortion. The ownership of the book was traced to a man who had been convicted of abortion in Hennepin County in 1941. When Miss Townsend was questioned by the authorities she denied that an abortion had been performed upon her by anyone, but when it was learned that she had previously stated that she had aborted herself the charge referred to above was placed against her.

✦ Reports and Announcements ✦

INTERNATIONAL ACADEMY OF PROCTOLOGY

The International Academy of Proctology announces its annual cash prize and certificate of Merit Award contest for 1953-1954. The best unpublished contribution on proctology or allied subjects will be awarded $100 and a Certificate of Merit. Certificates will be awarded also to physicians whose entries are deemed of unusual merit. This competition is open to all physicians in all countries, whether or not affiliated with the International Academy of Proctology. The winning contributions will be selected by a board of impartial judges, and all decisions are final.

The formal award of the first prize, and a presentation of other certificates, will be made at the annual convention dinner dance of the Academy in April, 1954. The Academy reserves the right to publish all contributions in its official publication, *The American Journal of Proctology*. All entries are limited to 5,000 words, must be typewritten in English, and submitted in five copies. All entries must be received no later than the first day of February, 1954. Entries should be addressed to the International Academy of Proctology, 43-55 Kissena Blvd., Flushing, New York.

* * *

Physicians are cordially invited to attend the sixth annual convention of the International Academy of Proctology to be held at the Palmer House, Chicago, Illinois, April 8 to 11, 1954.

An extensive motion picture seminar of proctologic surgery (including office techniques) will be held on April 11. All scientific papers will present the latest developments in proctology and gastroenterology.

Because general practitioners as well as gastroenterologists and proctologists, face proctologic problems in their daily practice, much of the program has been planned to answer their questions.

The program will be available upon request to the Executive Office of the International Academy of Proctology, 43-55 Kissena Boulevard, Flushing, New York.

MISSISSIPPI VALLEY MEDICAL SOCIETY 1954 ESSAY CONTEST

In its thirteenth annual essay contest the Mississippi Valley Medical Society will offer a cash prize of $100, a gold medal, and a certificate of award for the best unpublished essay on any subject of general medical interest (including medical economics and education) and of practical value to the general practitioner of medicine. Certificate of merit may also be granted to the physicians whose essays are rated second or third best. Contestants must be members of the American Medical Association and residents and citizens of the United States. The winner will be invited to present his contribution before the nineteenth annual meeting of the Mississippi Valley Medical Society to be held at Chicago, September 23 and 24, 1954. The Society reserves the exclusive right to first publish the essay in its official publication—the *Mississippi Valley Medical Journal*. All contributions shall be typewritten in English in manuscript form, submitted in five copies, not to exceed 5,000 words, and must be received not later than May 1, 1954. The winning essays in the 1953 contest appear in the January, 1954, issue of the *Mississippi Valley Medical Journal*. Further details may be secured from: Harold Swanberg, M.D., secretary, Mississippi Valley Medical Society, 209-224 W. C. U. Building, Quincy, Illinois.

INTERNATIONAL GROUP OF DOCTORS IN ALCOHOLICS ANONYMOUS

The fifth annual International Group of Doctors in Alcoholics Anonymous will meet at the Mayflower Hotel, Akron, Ohio, May 14 to 16, 1954. All physicians interested in this meeting are cordially invited to attend. For information and reservations, address: Doctors, Mayflower Hotel, Akron, Ohio.

MINNESOTA OBSTETRICAL AND GYNECOLOGICAL SOCIETY

New officers of the Minnesota Obstetrical and Gynecological Society were named at a meeting held December 5, at the Hotel Lowry, Saint Paul. Dr. Arnold O. Swenson, Duluth, vice president, succeeds Dr. Arthur B. Hunt, Rochester, as president; Dr. Leonard Lang, Minneapolis, was elected vice president, and Dr. Rodney F. Sturley, Saint Paul, was re-elected secretary-treasurer. Scientific papers were presented during the day sessions, and Dr. LeRoy A. Calkins, professor of obstetrics and gynecology at the University of Kansas Medical Center, Kansas City, Kansas, addressed the group in the evening.

POSTGRADUATE COURSE IN DISEASES OF THE CHEST

A postgraduate course sponsored by the Council on Postgraduate Medical Education of the American College of Chest Physicians will be conducted February 15 to 19, 1954, at New Orleans, Louisiana. The course will be held in conjunction with the Tulane University of Louisiana and the Louisiana State University. Dr. J. Winthrop Peabody is chairman of the postgraduate course committee. For further information, address American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

FAMILY DOCTORS' DAYS

University of Minnesota Hospitals

All physicians are cordially invited to attend the following Family Doctors' Days which will be presented under the direction of the department indicated.

February 17 — Neurology
March 10 — Dermatology
April 7 — Pediatrics

Activities begin with luncheon at 12:00 noon with the staff of the department in the Hospital Dining Room and will continue throughout the afternoon.

For further information, write the head of the department concerned or the Director, Department of Continuation Medical Education, 3330 Powell Hall, University of Minnesota.

(The initial Family Doctors' Day of the year was presented under the direction of the Department of Radiology, January 6, 1954.)

CONTINUATION COURSES

A *Conference on Coroners' Problems* will be presented by the University of Minnesota from March 8 to 10, 1954, at the Center for Continuation Study on the University Campus. Intended primarily for coroners, the course will also be of interest to law enforcement officers and to pathologists. Procedures of help in the investigation of all types of accidental or suspicious deaths will be discussed. The faculty for the course will include Dr. Walter W. Jetter, professor of legal medicine, Boston University, and the program will be presented under the direction of Dr. James McCartney, professor, department of pathology, University of Minnesota Medical School.

* * *

A continuation course in *Eye, Ear, Nose, and Throat for General Physicians* will be presented April 5 to 7 by the University of Minnesota at the Center for Continuation Study. The management of common problems involving the eyes, ears, and upper respiratory tract will be stressed. The course will be presented under the direction of Drs. L. R. Boies, Clinical Professor and Head, Department of Ophthalmology and Otolaryngology, and Erling W. Hansen, Clinical Professor and Director, Division of Ophthalmology. They will be joined by members of the clinical faculty of the University of Minnesota.

* * *

The University of Minnesota will present a continuation course in *Urology for General Physicians,* April 8 to 10, 1954, at the Center for Continuation Study. Common urological problems encountered by the physician in general practice will be discussed in detail. The course will be presented under the direction of Dr. C. D. Creevy, Professor and Director, Division of Urology, who will be joined by members of the faculty of the University of Minnesota Medical School and the Mayo Foundation.

* * *

Dr. Samuel A. Levine, Clinical Professor, Harvard University Medical School, Boston, will take part in a continuation course in *Cardiovascular Diseases for General Physicians* which will be presented at the Center for Continuation Study on the University of Minnesota Campus, March 22 to 24, 1954. The course, sponsored jointly by the University and the Minnesota Heart Association, will stress management of practical problems in the cardiovascular field. Dr. Levine will also present the annual George E. Fahr Lecture on March 23. The course will be presented under the direction of Dr. C. J. Watson, Professor and Head, Department of Medicine, University of Minnesota Medical School, and the remainder of the faculty will include clinical and full-time members of the faculty of the University of Minnesota Medical School and the Mayo Foundation.

* * *

A continuation course in *Emergency Surgery for General Physicians* will be presented at the Center for Continuation Study, April 1 to 3, 1954. Intended primarily for the physician in general practice, the course will stress the emergency management of various types of trauma and of acute abdominal conditions. The faculty for the course will include Dr. J. Garrott Allen, Professor of Surgery, University of Chicago School of Medicine. He will also deliver the annual Clarence M. Jackson Lecture on the evening of April 1. The program will be presented under the direction of Dr. O. H. Wangensteen, Professor and Chairman, Department of Surgery, with clinical and full-time members of the staff of the University of Minnesota Medical School.

BLUE EARTH VALLEY MEDICAL SOCIETY

Doctors of Martin, Faribault and Watonwan Counties (Blue Earth Valley Medical Society) held their annual meeting at the Presbyterian Church at Blue Earth, November 19, with the following officers elected: Dr. E. J. Bratrude, St. James, president; Dr. R. S. Armstrong, Winnebago, vice president; Dr. H. Boysen, Madelia, secretary-treasurer; Dr. M. P. Virnig, Wells, delegate; Dr. Harold Coulter, Madelia, alternate delegate, and Dr. William J. Hruza, Madelia, member of the board of censors.

RICE COUNTY MEDICAL SOCIETY

Officers of the Rice County Medical Society for 1954 were elected October 20 at Faribault, as follows: Dr. Norman Lende, Faribault, president; Dr. Paul F. Meyer, Faribault, vice president; Dr. Burton A. Orr, Faribault, secretary-treasurer; Dr. James J. Kolars, Faribault, delegate; Dr. R. R. Moses, Kenyon, chairman of censors, with Dr. F. W. Stevenson, Faribault, and Dr. R. F. Mears, Northfield, as the other members of the board of censors.

Committee chairmen for 1954 are: Dr. Burton A. Orr, Faribault, Committee on Military Affairs and Civil Disaster Medical Services; Dr. Heinz H. Bruhl, Faribault, Committee on Education; Dr. Paul F. Meyer, Faribault, Chest Pilot Study and Follow-up; Dr. E. J. Engberg, Faribault, County Medical Advisory Committee on Medical Service; Dr. Paul H. Weaver, Faribault, Committee on Public Health; Dr. Carl A. Traeger, Faribault, Committee on newspaper publications; and Dr. Bernard Street, Northfield, County Medical Advisory Committee to the Welfare Department.

Society meetings will be held regularly on the third Tuesday of each month during 1954.

In Memoriam

LEE WILLIS BARRY

Dr. Lee Willis Barry, long a distinguished Minnesota obstetrician and gynecologist, died at the age of sixty-seven in Fort Lauderdale, Florida, Thursday, December 3, 1953.

Dr. Barry had practiced for nearly thirty-four years in Saint Paul, but had moved his offices to the Minneapolis Medical Arts Building shortly before he died.

As assistant clinical professor of obstetrics and gynecology at the University of Minnesota and as a practitioner, Dr. Barry was a leader for many years in his specialty. He was the first to receive a Ph.D. degree in obstetrics and gynecology at the University of Minnesota.

He was born at Elbridge, Michigan, and received his pre-medical training and medical education at the University of Michigan. After a year's general internship at the St. Francis Hospital in Pittsburgh, Pennsylvania, he spent two years in postgraduate study in pathology at the University of Indiana. After a two-year interval, three additional years of obstetrics and gynecology study were spent at the University of Minnesota, from which he received his advanced degree in 1919. He located in Saint Paul in 1920.

Besides his University affiliation, Dr. Barry was a member of the Ramsey County Medical Society, the Minnesota State Medical Association, the American Medical Association, the Minnesota Academy of Medicine, the Saint Paul Surgical Society and the Minnesota Obstetrical and Gynecological Society. He was a fellow of the American College of Surgeons and the International College of Surgeons, and a diplomate of the American Board of Obstetrics and Gynecology and the American Academy of Obstetrics and Gynecology. He held the post of chief of staff at St. Joseph's Hospital in Saint Paul and was a member of Saint Paul Rotary Club, Sigma Xi and Phi Rho Sigma.

He is survived by his wife, Nora W. Barry; two daughters, Mrs. Harry Skornia, Champaign, Illinois, and Miss Margaret Barry, Minneapolis; one son, Dr. Lee W. Barry, Jr., Saint Paul, a dentist; one sister, Mrs. Russell Thomas, Owasso, Michigan, and three grandchildren. Honorary pall bearers were Drs. Joseph F. Bicek, G. D. Brand, Ben A. Weis, Earl Lowe and C. N. Hensel, all of Saint Paul.

PHILIP FRANCIS DONOHUE

Dr. Philip Francis Donohue, prominent Saint Paul urologist and 1953 president of the Ramsey County Medical Society, died at Miller Hospital in Saint Paul, Thursday, December 17, 1953, at 9:30 p.m., following a heart attack suffered a short time earlier at the St. Paul Curling Club.

Dr. Donohue was fifty-nine years old and had been active in his practice and in his favorite sports up to the time of his death.

He was born in 1895 in Saint Paul, where he attended grade schools, the St. Thomas Academy and Mechanic Arts high school. He took his premedical training at St. Thomas College and the University of Minnesota and received his medical degree from the St. Louis School of Medicine in St. Louis, Missouri. He served his internship at St. John's Hospital in St. Louis and at Miller Hospital in Saint Paul and took his postgraduate training in urology in the Department of Urology at Ancker Hospital, Saint Paul. He practiced his specialty as surgeon and diagnostician for thirty years in Saint Paul, where he served as staff urologist at Ancker, Miller, St. John's, St. Luke's and St. Joseph's Hospitals. He also served as associate professor of urology at the University of Minnesota.

Dr. Donohue was a fellow of the American College of Surgeons and a diplomate of the American Board of Urology, on which he also served as member of the board. He was a member of the North Central Section of the American Urological Association and of the Saint Paul Surgical Society, the Saint Paul Clinical Club, the Saint Paul Medical Forum and the Twin City Urological Society. He was a member of the Ramsey County Medical Society which he served in many capacities besides president, the Minnesota State Medical Association, and the American Medical Association.

Dr. Donohue occupied the old family home at 1481 Summit Avenue. He was an enthusiastic golfer and a member of Saint Paul Rotary Club, and of the Town and Country Club.

He is survived by one brother, John H. Donohue, of Saint Paul, and three sisters, Mrs. Grace Lavery, Evanston, Illinois; Mrs. Edith Dolan, Saint Paul, and Miss Florence Donohue, Pittsburgh, Pennsylvania.

ROBERT CYRUS FARRISH

Dr. Robert Cyrus Farrish died Friday, December 11, 1953, at his home in Sherburn after more than forty years of general practice in the area. He was eighty-six years old and still served occasionally as a consultant at the time of his death.

A community celebration marked his fortieth year of practice in Sherburn in 1950, and hundreds of residents from the entire district, most of whom he had delivered as infants, attended. It was the occasion for many recollections about him as the beloved and trusted country doctor. He was said to have cared for 1,600 cases during the influenza epidemic of 1917 and 1918 during which period he wore out four sets of tires, lost 44 pounds in weight, and drove to exhaustion no less than seven drivers for his car.

Dr. Farrish was born in Rockwood, Ontario, where his father, William Farrish, a Dumfries Scot, had located in the early 1850's. A friend of Empire-builder James

J. Hill, the elder Farrish moved to Saint Paul soon after Dr. Farrish was born in 1869. Dr. Farrish attended Rockwood Academy and then went to work for Hill in Saint Paul to help finance his medical education. He enrolled in the medical school of the University of Minnesota in 1897 and received his degree in 1901. He served his internship at St. Mary's Hospital in Rochester and became surgical assistant there to Dr. Charles H. Mayo. At the time of his death, he was the oldest living intern from St. Mary's.

He was a charter member of the Blue Earth County Medical Society, a member of the Minnesota State Medical Association, of which he became a life member in 1947, and of the American Medical Association. He served as vice president of the Minnesota Association in 1930.

Dr. Farrish went to Sherburn to practice with his brother, Dr. Malcolm Farrish, also a physician, in 1910, and together they maintained offices in Sherburn and Ceylon. After the death of his brother in 1915, Dr. Farrish practiced alone and also operated the Farrish Hospital in Sherburn for many years. In 1920, he married Mrs. Laura Bettenhausen Farrish, his brother's widow, and adopted her three children, the eldest of whom, Mrs. William Luwe, is now a practicing attorney in Mankato. A second daughter married Dr. L. O. Johnson, a Sherburn dentist. The third child is Dr. Robert Malcolm Farrish, a dentist practicing in Litchfield.

Dr. Farrish was a regional medical examiner for the 4-H clubs, and a 32nd degree Mason and member of the Shrine.

He is survived by his wife, three children, a sister, Mrs. L. G. Foley of Saint Paul, and two grandchildren.

HILLARD HERMAN HOLM

Dr. Hillard Herman Holm, for many years a leading surgeon of Glencoe, Minnesota, died following surgery for a stomach ailment at Asbury Hospital in Minneapolis, Thursday, November 19, 1953. He was sixty years old.

Dr. Holm had been active in his practice at Glencoe until a month before he died. He moved there on Valentine's Day of 1920, the day after his marriage to Blanche Laura Rucker of Howard Lake, and remained there continuously for thirty-three years.

He was born at Carver, April 11, 1893, and went to school there. He attended Macalester College where he received his Bachelor of Arts degree in 1915. He received his medical education at the University of Minnesota medical school and served a two-year internship in surgery at Minneapolis General Hospital.

During the earlier years of his practice, Dr. Holm operated his own hospital in Glencoe with the assistance of Mrs. Holm, a registered nurse. He was health officer of Glencoe and McLeod County for a number of years and served as coroner for several terms. He was a leader in civic as well as medical affairs in the community and was a member for many years of the First Congregational Church of Glencoe, the American Legion, the Izaak Walton League and the University of Minnesota Alumni Association.

Among physicians, he was recognized as a skilled surgeon, and he is remembered especially for a successful operation separating Siamese twins which was performed in January, 1927.

Dr. Holm was a fellow of the American College of Surgeons, a member of the Minnesota State Medical Association, the American Medical Association, the McLeod County Medical Society, the American Association of Railway Surgeons and the Milwaukee Road Company Surgeons.

He is survived by his wife; a daughter, Mrs. R. H. Rantala, Fort Worth, Texas; a brother, Harold C. Holm, St. Paul; and two grandchildren, Neil and Erick Rantala of Fort Worth.

Eleven fellow physicians from Glencoe and surrounding communities acted as honorary pallbearers. They were Drs. J. D. Selmo, Norwood; J. J. Smyth, Lester Prairie; A. M. Jensen and G. L. Griebie, Brownton; W. W. Klima, Stewart; Edward G. Olsen, Minneapolis; Charles G. Sheppard, Donald Brink, Walter G. Sahr and E. W. Lippman, Hutchinson; and C. W. Truesdale, Glencoe.

HENRY J. SHELVER

Dr. Henry J. Shelver, who practiced medicine first at Appleton and then in Ortonville for nearly thirty years, died Saturday, January 2, 1954, in the United States Veterans Administration Hospital in Fargo, North Dakota, where he had been a patient for the last three years. Dr. Shelver was sixty-nine years old.

He was educated at Concordia College in Moorhead and at Hamline and Northwestern Universities. He was graduated from the latter in 1910 and served his internship at Swedish Hospital in Minneapolis. After a further period of postgraduate work in Chicago, he opened his practice in Appleton where he remained for eight years before moving to Ortonville.

Until his retirement from active practice, Dr. Shelver was a member of the West Central Medical Society, the Minnesota State Medical Association and the American Medical Association.

Survivors are Mrs. Shelver and a daughter, Mrs. Glenn Crane of Morristown, New Jersey.

Of General Interest

Willow River, without a resident doctor since the death of Dr. W. C. Ehmke in 1948, has secured the services of **Dr. Martin S. Munson,** Barnum, for Tuesdays and Thursdays of each week. Willow River Community Club and Willow River Commercial Club have spent time and effort working out the details of the plan and securing office space for Dr. Munson.

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Dr. Fred Soper, New York City, director for the World Health Organization for the Western Hemisphere, in speaking at the University of Minnesota recently, cited the tremendous strides in helping backward countries help themselves to better health. Most significant has been the development of teams consisting of doctors, engineers, nurses, educators, sanitary inspectors and others who have worked together to fight perennial diseases such as malaria and yellow fever, and solve problems of mother and child health.

* * *

The quarterly new Fellows dinner, November 19, 1953, was held at Balfour Hall of Mayo Foundation House, with more than one hundred physicians in attendance. The dinner was given for new Fellows, and physicians recently returned from military service to complete their fellowships. Speakers were: **Dr. Fredrick A. Willius,** senior consultant in cardiology at the Clinic, who spoke of the heritage and traditions of the Mayo Clinic, and described experiences he had had with the late Dr. Henry S. Plummer; **Dr. Jesse Edwards,** consultant in pathological anatomy at the Clinic, who spoke of the opportunities for Fellows at the Mayo Foundation with regard to research activities, meetings and seminars, and the opportunities of obtaining postgraduate degrees.

Fellows were greeted by **Dr. Clayton H. Klakeg,** vice president of the Fellows Association and master of ceremonies for the program. The following officers were introduced: **Dr. E. V. Johnston,** president; **Dr. J. O. Godden,** secretary, and **Dr. E. B. Waldmann,** treasurer. **Dr. William Manger,** past president of the association, greeted the group also.

A standing ovation was given by **Dr. Donald C. Balfour, Sr.,** emeritus director of the Mayo Foundation, as he expressed his greetings.

* * *

Dr. Paul V. Cumiskey of Mankato, is temporarily working at the Oliver Clinic until a new clinic with which he will be associated in Minneapolis, is completed. Dr. Cumiskey is a graduate of the University of Minnesota, serving his internship at the Fresno County General Hospital.

Dr. M. H. Bauer, Winthrop, was injured by flying glass particles when a stray bullet hit the windshield of the car in which he and his wife were driving through Chaska, November 23. The shatterproof windshield protected him, probably saving his life. Mrs. Bauer was driving at the time of the accident.

* * *

The regents of the University of Minnesota authorized thirty-five new staff appointments, fifty terminations of staff personnel, eighteen promotions and transfers, twenty salary adjustments, twenty-eight leaves of absences, and accepted $28,744 in gifts. Two medical research scientists headed the list of appointments: **Dr. Francisco Grande,** citizen of Spain, will become an associated professor in the laboratory of physiological hygiene at the University, and **Dr. Richard W. Anderson,** psychiatrist from Saint Paul, will become an associated professor in the department of psychiatry and neurology.

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The merits of the Blue Cross and Blue Shield plans were discussed at the Stearns-Benton Medical Society meeting held at St. Cloud, November 19, 1953. **Dr. O. L. M. Nelson,** Minneapolis, a specialist in internal medicine, described cases of psychosomatic factors in treatment of diseases. Attendance prizes were won by **Dr. R. P. Koenig,** Paynesville, **Dr. M. McMahon,** St. Cloud, and **Dr. E. Sherwood,** Kimball.

* * *

The new Seifert-Dupont-Dornbach medical clinic, Excelsior, opened the first of November. The clinic contains some twelve consultation rooms and laboratories, and offices for the three physicians: **Dr. M. H. Seifert, Dr. J. A. Dupont,** and **Dr. Robert Dornbach.**

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Dr. Walter A. Reiling, chief of staff of the Good Samaritan Hospital, Dayton, Ohio, spoke at a general meeting of all Optimist clubs in Minneapolis, December 2. Dr. Reiling is president of Optimist International.

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Dr. John O'Hanlon has opened offices in Edina with **Dr. Harry C. Jensen.** Dr. O'Hanlon is a graduate of Marquette University. He has been in practice in rural areas as well as Minneapolis and Duluth.

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Dr. James Reinhardt, of Detroit Lakes, has been promoted to the rank of captain in the army. Dr. Reinhardt, stationed at James Connally Air Force Base, was surgeon and physician at Alexandria before going into the army.

Dr. Louis Katz, director of cardiovascular research at Michael Reese Hospital, Chicago, and professional lecturer in physiology at the University of Chicago, spoke on the brighter outlook for the victim of blood pressure at Saint Paul Society for Internal Medicine held at the University Club, December 2. **Dr. D. R. Gillespie,** of Saint Paul, is president of the group.

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Dr. Wallace Ritchie, Saint Paul, presented a discussion on head injuries with particular reference to neuro-surgical treatment which the general practitioner can render, at a dinner meeting of the Southwestern area of Minnesota Academy of General Practice. The meeting was held in the Municipal Lounge at Willmar, November 30.

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Dr. M. H. Larson, Nicollet, spoke at a Cancer Workshop held in St. Genevieve's Church, Lake Benton, November 18. Dr. Larson stressed that the doctor's office is the first line of defense against cancer.

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The fiftieth anniversary of the Hennepin County Tuberculosis Association which was organized December 2, 1903, as the Anti-Tuberculosis Committee of the Minneapolis Associated Charities, was celebrated at the Citizens Aid building, Minneapolis, December 2, 1953. **Dr. S. Marx White,** member of the association's executive committee, presided. He also gave a pictorial record of early tuberculosis work in Minneapolis and Hennepin County. "Tuberculosis led all other diseases as a cause of death. One child in every nine died before its first birthday," said Dr. White in commenting on the early work.

Dr. Stewart C. Thomson, professor and assistant director of the University of Minnesota School of Public Health, reviewed the work of a half century in fighting tuberculosis in a talk entitled, "The Building of a Wall."

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Dr. Martin S. Munson, Barnum, has "adopted" Kim Kyong Ja, an eleven-year-old Korean girl, under Foster Parents' Plan for War Children, Inc. The "adoption" is not legal, of course, only financial. The foster parent promises to contribute $15 monthly toward the child's support for one year, receiving in turn a brief history of the child and a photograph as well as correspondence, if possible, to help the child feel that he belongs to someone. "Home" to Kim Kyong Ja is a crowded institution in Kunsan.

* * *

Dr. Herman E. Hilleboe, son of P. S. Hilleboe, Mankato, has been named president-elect of the American Public Health Association. Dr. Hilleboe is state commissioner of health in New York. He will take office as president at the association's annual meeting to be held in Buffalo, New York, October, 1954.

Dr. Frederick W. Wittich, Minneapolis allergy specialist, has been named trustee and member of the executive committee of the newly-formed American Foundation for Allergic Diseases, Inc. This is a nonprofit organization to help promote understanding of allergic diseases, of which, studies have shown, there are 3,900,000 Americans suffering. Dr. Wittich is managing editor of *Annals of Allergy* and editor of the *Quarterly Review of Allergy and Applied Immunology.*

* * *

Dr. and Mrs. Arthur B. Williams, Saint Paul, celebrated their golden wedding anniversary in October. They were married in Rock Rapids, Iowa, October 14, 1903, and lived in Wilmont, Minnesota, where Dr. Williams practiced medicine until he was called into service in World War I. Following the war, the family moved to Worthington, where Dr. Williams practiced for six years, before moving to Saint Paul in 1926.

* * *

Dr. N. R. Kippen has become associated with the Breckenridge Clinic, Breckenridge. Dr. Kippen was graduated from the University of Manitoba in 1948. During the last five years he had further studies in surgery, orthopedic surgery and pathology in Canada.

* * *

Dr. Clinton C. Berg, Dr. Melvin G. Oppen and **Dr. Roger S. Johnson** are engaged in group practice with offices in both Excelsior and Deephaven. The association was formed December 1. Dr. Berg was previously associated with Dr. Lewis Reid of Excelsior. All three doctors are graduates of the School of Medicine, University of Minnesota.

* * *

Dr. Irvine McQuarrie, president of the State Heart Association, and **Dr. Harold S. Diehl,** dean of the University of Minnesota Medical School, were speakers at a luncheon in Coffman Memorial Union, December 5, for volunteer workers in the 1954 Heart fund. The annual fund campaign, to be held in February, with a quota of $210,000, is sponsored by members of the Minnesota State Association of Life Underwriters. A check of $30,000 was presented by the Minnesota Heart Association to Dr. Diehl at the luncheon. This is the second allocation for heart research at the university for 1953.

* * *

Dr. Joseph Brennan, Duluth, spoke at the Park Point Community Club, of Duluth, November 27. Dr. Brennan, born on the island of Malta, was studying medicine in Rome when he was imprisoned by the Italians during World War II. After escaping, he worked with underground groups. He completed his education in Europe and America.

* * *

The new Chisholm Memorial Hospital opened November 2, 1953, with **Dr. P. H. Macfarlane** as head of the staff; **Dr. Clarence Jacobson,** vice president, and **Dr. A. D. Klein,** secretary. Organized on

an "open staff" basis, the following doctors are registered with the hospital: **Dr. Joseph L. Arko, Dr. George Doxsee, Dr. George Erickson, Dr. Frank Farley, Dr. Bernard Flynn, Dr. Bayard French, Dr. Bernard Hapler, Dr. Robert Hansen, Dr. H. R. Irwin, Dr. Luverne Johnsrud, Dr. Stanley Lipinski, Dr. Robert Murray, Dr. Wilbert Parker, Dr. Andrew Sinamark, Dr. Carlyle Tingdale,** and **Dr. Wesley Tomhave.**

The thirty-bed hospital has twelve bassinets, operating and delivery room, and laboratory and x-ray facilities.

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Dr. B. J. Kennedy, University of Minnesota, spoke on "Medical and Chemotherapy Treatment for Cancer," at a luncheon meeting of the Ramsey County Cancer Society held at the Athletic Club, Saint Paul, November 18.

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Dr. H. J. Just was named chief of staff and **Dr. Carl A. Weiss,** secretary of the staff, at a recent meeting to name officers for the Hastings Memorial Hospital staff.

* * *

Dr. Malcolm M. Hargraves, member of the Mayo Clinic staff, known for his interest in soil conservation activities, was made an honorary member of the Soil Conservation Society of America at its national convention at Colorado Springs, Colorado, in December.

In 1948, Dr. Hargraves discovered the cell in human blood that made possible the diagnosis of lupus erythematosus.

* * *

Dr. Henry Ulrich, who helped found the Hennepin County Tuberculosis Association fifty years ago, was recently presented with a plaque in the form of the well-known emblem of the Anti-Tuberculosis Committee of the Associated Charities. The presentation was made by **Dr. S. Marx White** at a luncheon held in Dr. Ulrich's honor at the Citizens Aid Building, Minneapolis.

* * *

At a meeting of the Red River Valley Medical Society, held in Thief River Falls, November 24, **Dr. Davitt A. Felder** of University of Minnesota, spoke on "Diseases of the Blood Vessels." Following the dinner, wives of the doctors met for a short auxiliary meeting at the home of **Dr. and Mrs. William A. Feigal.**

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Dr. Joseph C. Michael and **Dr. John W. Schumacher** have been associated in the practice of psychiatry and neurology at the Medical Arts building, Minneapolis, since December 1.

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Dr. John G. Freeman, clinical director of the Fergus Falls State Hospital for the past two and a half years, has accepted a similar position with the State Hospital in Jamestown, North Dakota, where he will take over his new duties February, 1954.

Dr. Freeman participated as speaker at the fall meeting of the executive secretaries of the Minnesota Welfare Boards at the University of Minnesota Center for Continuation Study recently. He was also guest speaker at the American Public Welfare Association's session on "Community Planning for the Care of the Senile Patient" held in Chicago, Illinois, December 5.

* * *

Dr. Donald J. McNairy, Phoenix, Arizona, spent the week of December 7 to 11 in Chicago as a member of the teaching staff at the annual meeting of the American Academy of Dermatology and Syphilology, his subject being "Medical Photography." Dr. McNairy received his Master of Science degree in Dermatology and Syphilology at the University of Minnesota in 1944.

* * *

Dr. and Mrs. B. J. Cronwell, Jr., Austin, **Dr. Herman Miller,** Grand Meadow, and **Dr. P. J. Schneider,** Adams, met at the home of **Dr. Thomas M. Seery** in Austin, November 23, to take the first steps in organizing the Mower County Heart Council. Dr. Seery, designated acting chairman of the Minnesota Heart Association, said the object of the council will be to distribute vast amounts of educational material available through the Heart Association. The group plans a larger meeting for January in which civic and farm groups will be represented.

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Dr. Moses Barron, Minneapolis, discussed developments in the Middle East at a general meeting of the Minnesota Emergency Committee on Israel of the Saint Paul Zionist district, in the Jewish Community Center, November 17.

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Dr. Deane W. Benton, formerly of New Ulm, now specializing in psychiatry in Minneapolis, gave an illustrated talk on a "Laymen's View of Psychiatry" at a Rotary Club meeting held November 17 at the Silver Latch Cafe in New Ulm.

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At the organization meeting of the "Catholic Physician's Guild," held in St. Cloud, November 30, with approximately thirty-five doctors in attendance, **Dr. W. T. Wenner,** St. Cloud, was elected president; **Dr. F. J. Schatz,** St. Cloud, vice president; **Dr. W. F. Skaife,** Little Falls, secretary, and **Dr. J. B. Gaida,** St. Cloud, treasurer.

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Dr. Irvine McQuarrie, Professor of Pediatrics at the University of Minnesota Medical School, has been named one of tthe recipients of the 1954 Modern Medicine Award for Distinguished Achievement, Dr. Walter C. Alvarez of Minneapolis, editor-in-chief of the magazine, has announced. His contributions to the understanding of metabolic disturbance in children earned the award for Dr. McQuarrie. The awards are presented annually by *Modern Medicine* in recognition of significant work in the advancement of medical practice.

Dr. C. A. Undine, Minneapolis, attended the midwest regional meeting of the American College of Physicians at Milwaukee, Wisconsin, November 21, 1953.

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Dr. G. S. Boyer, Crookston, radiologist for the Northwestern Clinic at Crookston, addressed Roseau physicians, recently, on "Infertility Studies."

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Dr. John L. Delmore, Jr., Roseau, attended the orthopedics course at the Center for Continuation Study at the University of Minnesota, November 16 to 18, 1953.

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Dr. A. C. Hilding, Duluth, was recently elected to membership in the Kunglia Fysiografiska I. Lund, honorary Swedish scientific organization which limits its membership to approximately 100 Swedish and 100 foreign members.

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Dr. Louis L. Freidman, Saint Paul, participated in a symposium on "Surgery in Sterility" presented by the Western Division of the American Sterility Society in Palm Springs, California, November 6 to 8, 1953. Dr. Friedman also addressed the Lynn County Medical Society at Cedar Rapids, Iowa, November 12, on "Management of the Infertile Couple."

* * *

Dr. Robert S. Abernathy, Fellow in the Department of Medicine at the University Hospitals, Minneapolis, has been awarded a Research Fellowship in Medicine by the American College of Physicians. The appointment is effective July 1, 1954. He will work under the preceptorship of Dr. Wesley W. Spink, Professor of Medicine, on the pathogenesis of brucellosis. Dr. Abernathy is a graduate of Duke University School of Medicine. He interned in the University of Minnesota Hospitals, and following a year as Fellow in Medicine, he served two years in the army in Korea. Dr. Abernathy's wife, Dr. Rosalind Abernathy, is a part-time assistant in the Department of Pediatrics at the University Hospitals.

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Dr. R. L. Parsons, formerly of Monterey, is now located in Glencoe, Minnesota, for the practice of medicine and surgery.

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Dr. George H. Olds, New Richland, has been named a member of the Mental Health Clinic, which has its main office in Albert Lea.

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Dr. E. F. Beyer, Braham, called into the army from his medical practice in May, has been promoted to the rank of captain. Dr. Beyer has been stationed with the Seventh Division in Korea since August.

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Dr. Milton Moore Howell, previously in charge of a fifty-bed medical ward at the United States Public Health Hospital, Norfolk, Virginia, is now associated with **Dr. C. W. Truesdale** in the operation of the Glencoe Clinic. Dr. Howell is a graduate of the University of Rochester School of Medicine, Rochester, New York. Prior to his entering medical school, Dr. Howell was in the army from 1940 until 1945. Starting as a private he left the service a major.

* * *

Dr. George W. Snyder, Saint Paul, trustee of the American Legion's Hospital Association, pointed out at the opening session of the Minnesota fall conference, that dues allotted from membership fees are not sufficient to sustain the hospital program to be carried out by the association. This program, for wives and dependents of veterans who are financially unable to provide hospital care for their families, receives twenty-five cents of each member's dues, and five cents from each auxiliary member. Dr. Snyder urged formation of programs to raise funds for the association, especially during hospital week in February.

* * *

Dr. Raymond L. Page, St. Charles, was presented a merit award at the annual refresher course of the State General Practice Academy held at Hotel Lowry, Saint Paul, November 4. **Dr. Charles C. Cooper,** Saint Paul, is president of the group, which this year had more than 500 physicians in attendance at the sessions.

* * *

Dr. Louis Loes, who recently opened an office in St. Cloud for specialization in obstetrics, spoke at a meeting of the United Cerebral Palsy group of Central Minnesota, held in St. Cloud, December 12. He discussed problems of pre-natal care and delivery from the cerebral palsy viewpoint.

MINNESOTA BLUE CROSS-BLUE SHIELD

Of interest to all participating physicians are the improvements in both the present standard Blue Shield contract and its schedule of payments, which have been approved by the Board of Directors, for services rendered Blue Shield subscribers on and after January 1, 1954. In addition to these changes in the present standard contract, the Board expects to have a second contract with higher fees and higher service benefit annual income levels available for the public soon after March 1, 1954. The changes in the standard contract and fee schedule are the result of the Board's policy of improving the contract as rapidly as possible.

Dual Contract and Fee Schedule

A new standard contract and schedule of payments incorporating these improvements have been prepared. In the new contract will be clauses applying to the present standard contract, which will be known as Plan A, and also clauses pertaining to the new, higher fee, higher service benefit income contract, which will be known as Plan B. Principal differences in the two plans will be the fees paid and the annual incomes which determine eligibility for service benefits.

Although the new Plan B contract is not to be available to the public before March 1, 1954, in order to avoid duplication of printing and other costs, a new fee schedule containing both Plan A and Plan B fees has been prepared for early mailing to all participating physicians. Misunderstandings and other difficulties will be avoided if it is borne in mind that fees listed in the new schedule in the column headed "Fee Schedule B" do not apply to the present, or Plan A, contract.

Benefit Increases in Present Standard Contract

Service benefit annual income levels of the present contract are to be increased on January 1, 1954, from $2,000 to $2,400 for single subscribers and from $3,000 to $3,600 for family subscribers. It is believed that the increases in fees compensate physicians for providing service benefits for subscribers with these higher incomes. Prior to January 1, 1954, these annual income levels for service benefits are $2,000 and $3,000 for single and family subscribers, respectively.

When both husband and wife have a single contract, the annual income level which determines eligibility for service benefits will be the combined annual income of the family, and not the income based on the type of contract. Ambiguity has previously existed on this point. On July 1, 1953, this interpretation was approved by the Board of Directors and the contract is now being changed in this manner to clarify this ambiguity.

While the clause in the contract pertaining to in-hospital medical care limits such care, or combined medical and surgical care for the same condition, to thirty days at present, it is being changed to cover seventy days of such services rendered on and after January 1, 1954. As a result of this change, after January 1, 1954, as much as seventy days of care, instead of the present thirty days, will be provided each twelve months for every unrelated eligible condition or illness.

Waiting periods in the present group contract involving benefits for maternity care, pre-existing conditions, tonsillectomies and adenoidectomies for minor dependents, and for these and herniotomies and hemorrhoidectomies in the present non-group contract are of ten months' duration. These waiting periods are being decreased in the contract to only nine months on and after January 1, 1954. In other words, while claims for these conditions have not been eligible for payment until the subscriber has had a Blue Shield contract for ten months, claims for services rendered for these conditions on and after January 1, 1954, will be valid after the contracts are only nine months old.

Under the present contract, circumcisions are not valid claims unless the child is at least one year old. This will be changed so that circumcisions performed on and after January 1, 1954, will be eligible for payment in accordance with the fee schedule if done after the date of discharge of the mother from the hospital following the obstetrical delivery.

At present, services performed by dentists have not been valid Blue Shield Claims. Services performed by licensed dentists in Minnesota on and after January 1, 1954, in the treatment of jaw fractures, dentigerous cysts, adamantinomas, oral and extra oral drainage of alveolar abscesses will be eligible for Blue Shield allowances in accordance with the contract. Previously, such services covered by the contract were eligible for Blue Shield payment only when performed by a doctor of medicine.

Benefit Increases in the Present Schedule of Payments

In addition to the benefit improvements written into the present standard contract, an extensive revision of its fee schedule has made available more liberal allowances in surgical, medical and maternity care. In fact, of a total of ninety-five changes in the fee schedule, fifty-eight consist of fee increases, new items not listed before, or revisions of the method of payment. Most of the remaining changes represent bringing the description of the items up-to-date with present-day medical or surgical practice.

Especially important are twenty-seven distinct fee increases for different types of medical-surgical-obstetrical care. Of these, seventeen are for surgery and include $50 increases for seven difficult and more costly operations, and 10 increases in fees for recently developed and frequently performed operations. Also, six increases are for in-hospital medical care. Not only are benefits for each of the first two days of both routine and emergency in-hospital medical care being increased, but the total period of in-hospital medical care or combined in-hospital medical and surgical care for the same condition is being increased from thirty to seventy days for each period of twelve consecutive months. Maternity benefits are also being increased from $50 to $60, and three increases in anesthesia benefits are included.

Of the remaining changes, two are of particular importance to participating physicians. For treatment of sprains or strains on or after January 1, 1954, a fee of $5.00 is listed and this will permit allowances for the x-ray necessary for their diagnosis, in accordance with the contract. Also, circumcisions which have been excluded from benefits till the child is twelve months old, when performed after the date of the mother's discharge, and after January 1, 1954, will be eligible for a $10 fee till the child is three months of age, and a $15 fee from three months to six years of age. In addition to these increases, fourteen other new items are being added, and fifteen changes are being made to improve the methods of paying for foreign body removal, lacerations, burns and other surgical procedures.

No Increase of Rate for Present Standard Contract

All of these many improvements in the present contract and the schedule of payments are being made without any increase in the rate or cost of the present contract to the subscriber. These increased benefits mean several hundred thousand dollars more in benefits paid for subscribers' medical, surgical and maternity care each year. Improving the benefits without increasing the rates clearly demonstrates the Board of Directors' desire and intention of providing the greatest benefits at the lowest possible cost. This course of action is possible only with the full support and co-operation of all members of the medical profession.

BOOK REVIEWS

Books listed here become the property of the Ramsey, Hennepin and St. Louis County Medical Libraries when reviewed. Members, however, are urged to write reviews of any or every recent book which may be of interest to physicians.

BOOKS RECEIVED FOR REVIEW

SALT AND THE HEART. Edward T. Yorke, M.D. Attending Cardiologist, Alexian Brothers Hospital, Associate Cardiologist, St. Elizabeth Hospital, Dispensary Physician, Elizabeth General Hospital, Elizabeth, N. J.; Consultant in Medicine, Rahway Hospital, Rahway, N. J. 83 pages. Illus. Price $3.45, cloth. Linden, N. J.: Drapkin Books, 1953.

MENTAL HEALTH IMPLICATIONS IN CIVILIAN EMERGENCIES. Report of Subcommittee on Civil Defense, Community Services Committee, National Advisory Mental Health Council, May, 1953. 25 pages. Price 15c, paper cover. Washington, D. C.: U. S. Government Printing Office, 1953.

REVIEW OF PHYSIOLOGICAL CHEMISTRY. 4th Edition. Harold A. Harper, Ph.D. Professor of Biochemistry, University of San Francisco; Biochemist Consultant to Metabolic Research Facility, U. S. Naval Hospital, Oakland; Biochemist Consultant to St. Mary's Hospital, San Francisco. 328 pages. Illus. Price $4.00, paper cover. Los Altos, Calif.: Lange Medical Publications, University Medical Publishers, 1953.

A PRIMER OF CARDIOLOGY. By Geoge E. Burch, M.D., F.A.C.P., Henderson Professor of Medicine, Tulane University School of Medicine; Physician-in-Chief, Charity Hospital; Consultant in Cardiovascular Diseases, Oschner Clinic; Visiting Physician, Tuoro Infirmary, New Orleans. Second Edition. Thoroughly Revised, with 214 Illustrations, 339 pages. Cloth, $5.50. Philadelphia: Lea & Febiger, 1953.

This book is intended as a guide to the student's early clinical studies of heart disease, according to the author's preface. It is provocative and it emphasizes the use of physiological data plus logic to solve selected clinical problems. I am afraid this is not the publisher's concept of the book since he refers to it as "comprehensive in scope . . . (a) complete presentation . . . (with) emphasis on problems (of) daily practice." A modern book relating to cardiology is hardly complete if it contains not a single electrocardiogram. It is not emphasizing daily problems if it devotes fourteen pages to calculation of congenital shunts and three to angina.

The prospective buyer of the book, having in mind the author's classic monograph on electrocardiography which is similarly titled, is not likely to realize how little clinical wisdom he is purchasing. The electrocardiographic book is a primer and is practical and helpful to the practitioner. The volume being reviewed is none of these.

Even as a guide to the student the book has serious defects. For example, contrasting theories of congestive failure are presented, but the essential points of the theories are controverted in the telling. This surely is a postgraduate presentation of an interesting sort, but must be bewildering to the beginner. So much is made of physiological facts and graphs and so much stress is placed on the imperative need of more reliable data of a similar sort that the reader might not realize very notable clinical experiments have been presented in recent years directly beneficial to the science of cardiology: for example, the precise assessment of virtue in modes of treatment in infarction and the quantitative role of electrolytes in the failing heart. The medical student should be progressing steadily and rapidly to clinical considerations. Books can help, but a shiny display of mathematical formulae related to heart sounds, a forensic presentation of the author's attitudes on congestive failure (page 56), and an individualistic assessment of new techniques such as catheterization (page 219) are not likely to hasten the maturity we all yearn for.

The author's insistence on severe anemia as a sign of heart disease (meaning the latter is always present with former) and on classifying functional heart complaints as heart disease will antagonize many readers.

The pages contain some excellent discussions. The treatment of functional complaints is handled in a manner that suggests the vast clinical experience of the author. The discussion of tracheal tug in aneurism is one of the clearest the reviewer has read.

For the teacher of cardiology, even though a casual and informal one, the book should be useful. It is factual and it is an attempt at the correlation much discussed of basic science and medicine. For the student of undergraduate rank, truly physiological or clinical monographs are more suitable. For the practitioner, the book will be disappointing if not misleading. So much excellent writing has been done on heart disease it would be easy to employ the few idle hours in a busy life to better advantage.

W.B.M.

DISEASES OF WOMEN. By Robert James Crossen, A.B., M.D., F.A.C.S., Assistant Professor of Clinical Gynecology and Obstetrics, Washington University School of Medicine, Section Head of Unit Obstetrics and Gynecology, St. Louis City Hospital; Assistant Gynecologist and Obstetrician to Barnes Hospital. 10th ed. 935 pages. Illus. Price $18:50 (cloth). St. Louis: C. V. Mosby Co., 1953.

It is indicative of passing time that the new tenth edition of Diseases of Women for the first time bears the name of only one Crossen. Dr. Robert J. Crossen, as sole author, has accomplished a difficult task well. To revise a standard text, to bring it up to date and still maintain the same degree of excellence and completeness for which the original manuscript long has been known, is a monumental project. The new author, with his deletions and additions has greatly improved this already well-known book. Removing many of the pages devoted to operative gynecology, allied fields such as gastroenterology, and pathology remote from that of gynecology has not, as one would expect, made the text less complete but rather allows space for the addition of more pertinent and up-to-date data. The addition of Willard Allen's chapter of "Endocrine Control and the Ovarian Cycle," A. N. Arneson's detailed yet clear explanation of radiation therapy in cervical cancer, and the treatise on the psychosomatic aspects of gynecology

from a down-to-earth viewpoint has greatly augmented the value of the book to student and practitioner alike.

Diseases of Women continues to be one of the most complete books of its kind. One seldom finds a more complete review of the anatomy, embryology, and physiology of pelvic organs even in texts devoted exclusively to those specific fields. Biochemistry and its relation to pelvic physiology is very detailed, more so than perhaps is necessary in a book of this character. The unusual section devoted to pitfalls in gynecological diagnosis alone should guarantee this edition a respected place on the shelf of the specialist as well as the general practitioner.

Perhaps this very completeness reveals itself as the only criticism the new edition demonstrates. To be used as a reference the countless paragraphs on theory of etiology, related physiology and embryology may prove to be a disquieting barricade. As a text for the student, a complete study reference for the specialist, and a thorough approach to diagnosis and treatment for the practitioner, Diseases of Women equals all and surpasses many comparable gynecological texts.

RICHARD R. FLIEHR, M.D.

MAY'S MANUAL OF THE DISEASES OF THE EYE FOR STUDENTS AND GENERAL PRACTITIONERS. Revised and edited by Charles A. Perera, M.D., Associate Clinical Professor, College of Physicians and Surgeons, Columbia University, New York. 21st ed. 512 pages. Illus. Price $6.00. Baltimore: Williams & Wilkins Co., 1953.

The new twenty-first edition of May's Ophthalmic Manual maintains its high standing of efficiency in describing eye diseases and the latest treatments for them. The various ophthalmic operations are described and illustrated, including the newer ones for cataract, glaucoma and detachment of the retina. The book can be recommended not only for the student and practitioner, but also for the specialist.

E. R. BRAY, M.D.

LIVING WITH A DISABILITY.—At Home—At Work—At Play. By Howard A. Rusk., M.D., and Eugene J. Taylor, in collaboration with Muriel Zimmerman, O.T.R., and Julia Judson, M.S. 191 pages. Illus. Price $3.50. New York: The Blakiston Co., Inc., 1953.

Dr. Rusk has had a great deal of experience with disabled people and has followed numerous cases for long periods of time. In this book he has brought out some of the means of help, which are simple in many cases and more complicated in others, but which will aid the person to be more independent. Many of the suggestions that he has, and has well pictured for physical aids, could be made in any home work shop and many of them could be varied slightly to fit the individual case.

The text of the book is interesting and easy reading, and the pictures are all largely self explanatory. It would be advisable for all doctors, and especially those who have patients with disabilities, to carefully review this book and use it as a reference for suggesting different types of aids to the handicapped.

JOHN C. FEULING, M.D.

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